A HOSPITAL BASED CROSS-SECTIONAL STUDY ON THE PREVALENCE OF VARIOUS HAEMOTOLOGICAL ABNORMALITIES IN PATIENTS WITH DECOMPENSATED CHRONIC LIVER DISEASE

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CERTIFICATE

This is to certify that the Dissertation entitled **"A Hospital Based Cross-Sectional Study On The Prevalence Of Various Haemotological Abnormalities In Patients With Decompensated Chronic Liver Disease",** herewith submitted by **Dr.Irfan Ismail Ayub,** Post Graduate in General Medicine, Chengalpattu Medical College to the Tamilnadu Dr. M.G.R. Medical University is a record of a bonafide research work carried out by him under my guidance and supervision from Sept 2010 to Nov 2010.

Prof. and Unit Chief

Prof. and Head
Department of Medicine

DEAN

DECLARATION

I solemnly declare that the Dissertation titled **"A Hospital Based Cross-sectional Study On The Prevalence Of Various Haemotological Abnormalities In Patients With Decompensated Chronic Liver Diseases ",** was done by me at Chengalpattu Medical College & Hospital during the period from Sept 2010 to Nov 2010 under the guidance and supervision of Prof.Dr.K.E.Arumugam and Prof. Dr. S.Penicilliah.

This dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch I) in General Medicine.

Place : Chengalpattu **Dr. Irfan Ismail Ayub**

Date :

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CONTENTS

INTRODUCTION

Hematopoiesis is the process by which the formed elements of the blood are formed. The process is regulated through a series of steps beginning with the pluripotent hematopoitic stem cell. Stem cells are capable of producing red cells, all classes of granulocytes, monocytes, platelets, and the cells of the immune system.[1]

An introduction to the liver cannot go without mentioning that it is the largest organ of the body, weighing about 1 to 1.5 kg, and representing 1.5 - 2.5 % of the lean body mass. Liver is located in the right upper quadrant of the abdomen. It receives dual blood supply; 20% from the hepatic artery and 80% from the portal vein. Physiologically, the majority of cells in the liver are the hepatocytes (2/3rds); the remaining cells are the Kupffer cells, stellate cells, endothelial cells, blood vessels, bile ductular cells and supporting structures.[2]

The relationship between the hematopoietic system and the hepatic system in the human body dates back to the intrauterine period where the latter acts as a haemotopoietic organ and functions as the producer of the former.

Hepatocytes perform numerous and vital roles in maintaining homeostasis. These functions include synthesis of essential serum proteins (albumin, carrier proteins, coagulation factors), the

production of bile and its carriers, the regulation of nutrients like lipids, cholesterol, glucose).[2] Albumin and other carrier proteins have a role in homeostasis. Globulin is required in the synthesis of heamoglobin. The coagulation factors produced by the liver play important roles in preventing a tilt in the precarious balance held between bleeding and thrombosis. Bilirubin is a by-product of heme breakdown. Nutrients like cholesterol and lipids are needed in the synthesis of the blood cells. From the above information, it is not difficult to see the inter-relationship between the hepatic and the hematopoietic systems.

It is known that the hormone Erythropoietin is required for red cell production. Erythropoietin is not only produced by the peritubular capillary lining cells in the kidney, it is also produced by hepatocytes.[1] Liver is the storage site for iron, vitamin B_{12} and folic acid which are necessary for normal hematopoiesis.[3,4]

It is now understood chronic liver disease presents with haemotological abnormalities. It is worth mentioning that other than liver disease per se, the complications following chronic liver disease contribute to haemotological disturbances. Such complications include G.I bleed secondary to portal hypertension, hyperspenism, hemolysis and malnutrition.[5]

It is not unknown to clinicians that the routine liver function tests always incorporate serum bilirubin, serum albumin and prothrombin time. As mentioned above, derangements in the values of the above parameters gives us an idea of the disturbances in the haemotopoietic system. When the liver is damaged by either acute or chronic disease, abnormalities in the haemotopoietic system follow suit.

The hematological abnormalities in a chronic liver disease add morbidity to the primary pathology and increase the mortality. Hence it becomes imperative to investigate the hematological abnormalities to decrease the co-morbidity.

AIM OF THE STUDY

1. To identify the various hematological abnormalities in patients with decompensated chronic liver disease .
2. To find out the prevalence of these haemotological abnormalities within the study group.
3. To identify whether certain haemotological abnormalities are more associated with chronic liver disease patients.

REVIEW OF LITERATURE

LIVER

The anatomical and physiological aspects of the liver have already been reviewed earlier. Pathological disease of the liver can be either acute or chronic. Chronic liver disease is characterized by cirrhosis. Cirrhosis of liver is defined histopathologically; it consists of the development of fibrosis to the point that there is architectural distortion with the formation of regenerative nodules.[6] This results in loss of hepatic mass and function with an alteration in blood flow. The induction of fibrosis occurs with activation of hepatic stellate cells.[6]

Clinically, such patients with cirrhosis of liver can present in a compensated or decompensated form.

Table – 1 –Some Causes of Cirrhosis[6]

Alcoholism	Cardiac Cirrhosis	NASH
Chronic Viral Hepatitis	Hemochromatosis	A_1 AT Deficiency
Autoimmune hepatitis	Wilson's disease	Cystic Fibosis

COMPENSATED CIRRHOSIS[7]

Compensated cirrhosis is discovered at routine examination or biochemical analysis with or without external signs and symptoms of liver failure. They may present with nausea, vomiting, indigestion, flatulence or dyspepsia. It may be suspected in patients with spider

angiomas, palmar erythema, unexplained epistaxis or edema of ankles.

Clinically firm enlargement of liver and Splenomegaly may be present. There may be a slight increase in serum transaminase or γ Glutamyl Transferase level[7].

DECOMPENSATED CIRRHOSIS

Patients who have developed complications of cirrhosis are said to have decompensated liver disease.[6] Signs of liver cell failure like ascites and jaundice are present in patients with Decompensated liver disease.

Table 2 - Complications of Cirrhosis[6]

Portal hypertension	Hepatopulmonary syndrome
Variceal bleed	Malnutrition
Splenomegaly and hypersplenism	Coagulopathy
Ascites and SBP	Bone disease
Hepatorenal syndrome	
Hematological abnormalities; anemia, hemolysis, thrombocytopenia, neutropenia	
Hepatic Encephalopathy	

HAEMATOLOGICAL ABNORMALITIES AND CHRONIC LIVER DISEASE - REVIEW OF PREVIOUS LITERATURE

I) DISORDERS OF RBC

ANAEMIA

Anaemia of diverse etiology occurs in 75% of patients with chronic liver disease.[8] The causes of anaemia can be studied under various etiologies :

1. Portal Hypertension

Acute gastrointestinal hemorrhage is a common and potentially serious complication of portal hypertension[9,10,11,12]. It is usually caused by rupture of an esophageal varix. Hemorrhage caused by this mechanism is the second most common cause of mortality in patients with cirrhosis. In such patients, a ruptured esophageal varix is the cause of approximately 70% of episodes of upper gastrointestinal hemorrhage[10]. Acute hemorrhage may induce severe hypovolemia and subsequently secondary iron deficiency anemia.

The initial aim of treatment is correction of hypovolemia and restoration of stable hemodynamic function; minimal values for mean arterial pressure and for haemoglobin of 80 mmHg and 8 g/100 mL, respectively, should be maintained. Initially, gelatin-based colloids or solutions of human albumin may be infused to correct

hypovolemia. However, infusions of packed erythrocytes in plasma are ideal in this context since such infusions have the potential of correcting, not only hypovolemia, but also secondary anemia. First-line management involves institution of medical therapy; administration of vasoactive drugs, such as somatostatin, octreotide or terlipressin; and optimal endoscopic treatment involves ligation of esophageal varices and obturation of gastric varices with tissue adhesives.

In some patients with cirrhosis, chronic hemorrhage into the gastrointestinal tract occurs. Esophageal, gastric varices and portal hypertensive gastropathy may be associated with slow chronic loss of blood into the gut and development of chronic iron deficiency anemia.

The most important approach to management is prevention of variceal hemorrhage[9,11,12]. The annual incidence of initial variceal hemorrhage in patients with cirrhosis is estimated to be about 4%, but for the group with medium-sized or large varices, the incidence is about 15%[10]. β-blockers or isosorbide 5-mononitrate may reduce the rate of transformation of small varices into large varices and decrease the incidence of variceal hemorrhage in patients with small varices[9].

The risk of recurrent hemorrhage is > 60%. Accordingly, all patients surviving variceal hemorrhage should receive active treatment aimed at preventing recurrence. Nonselective β-blockers or isosorbide 5-mononitrate and endoscopic therapy, including ligation of and/or sclerotherapy of varices, are the first-line treatments for preventing recurrence of variceal hemorrhage[9,12]; a combination of both these approaches constitutes optimal management.

Additional treatment with oral iron supplementation is indicated for iron deficiency anemia caused by chronic blood loss. In some cases of advanced chronic liver disease, intravenous iron formulations may be administrated to increase plasma levels and tissue deposits of iron.

2. Hypersplenism

Hypersplenism secondary to portal hypertension is another mechanism of anemia in patients with chronic liver disease. Hypersplenism is associated with splenomegaly. In addition to chronic liver disease, thrombosis of the splenic vein may also be a cause of an increase in pressure within the portal venous system,

which can lead to secondary hypersplenism.

The main characteristics of hypersplenism are those attributable to pancytopenia. Hemolytic anemia occurs because of intrasplenic destruction of erythrocytes. Destruction of megakaryocytes and leukocyte precursors results in thrombocytopenia and leukopenia[13].

Symptoms and signs of hypersplenism are influenced by the primary underlying disease; they include abdominal pain and/or discomfort, and, in advanced cases, gastrointestinal hemorrhage secondary to portal hypertension. There may be hyperplasia of the progenitor cells in the bone marrow.

It is important to determine the cause of hypersplenism. The main therapeutic approach for this syndrome is management directed at the underlying primary disease, usually chronic liver disease. When chronic liver disease is advanced, additional therapeutic options may need to be adopted. After assessing the severity of impaired hepatocellular function in a patient with advanced chronic liver disease, splenectomy may be considered if the splenic vein is thrombosed. An alternative approach is partial or total embolization of the splenic artery, which, in some recent studies, has been associated with good results, in particular, lower morbidity and mortality rates than those associated with surgery. Partial embolization preserves the immunological function of the spleen and is the preferred option for patients with cirrhosis[14].

3. Aplastic Anaemia

Aplastic anemia associated with liver disease is characterized by development of pancytopenia and hypocellular bone marrow in relation to the occurrence of hepatitis[15]. The main feature of this syndrome is injury to or loss of pluripotent hematopoietic stem cells, in the absence of infiltrative disease of the bone marrow[15,16,17,18]. Hepatitis-associated aplastic anemia (HAA) has been defined as a variant of aplastic anemia, which occurs concurrently with or within 6 months of an increase in the serum level of alanine aminotransferase to at least five times the upper limit of the reference range.

Severe marrow aplasia may be induced by hepatitis viruses, such as hepatitis B virus and hepatitis C virus (HCV), and also by other viruses, such as human immunodeficiency virus, Epstein-Barr virus, transfusion-transmitted virus and echovirus[15,19]. Parvovirus B19 commonly infects pro-erythroblasts and may induce transient red –cell aplasia, particularly in patients with chronic haemolytic anemia. It has been postulated that viruses and/or antigens, through the mediation of γ interferon or the cytokine cascade, induce lymphocyte activation and ultimately apoptotic death of hematopoietic cells in the bone marrow[16].

Clinical presentation includes symptoms and signs related to pancytopenia, such as pallor, fatigue, hemorrhagic manifestations, progressive anemia, and bacterial infections.

The diagnosis of HAA is suggested by a complete blood count, which reveals pancytopenia (including anemia) together with absolute reticulocytopenia[15]. A bone marrow biopsy typically reveals hypocellularity that affects red and white cell precursors and megakaryocytes; residual hematopoietic cells appear morphologically normal[18].

The two major options for treating severe HAA are hematopoietic cell transplantation and immunosuppressive therapy. According to recent reviews, response rates to these approaches are 75%-88% and 75%-80%, respectively[15,17]. Blood and platelet infusions are often necessary before instituting specific treatment; before administration, blood products should be irradiated to avoid sensitization.

4. Anaemia Secondary to Treatment of Hepatitis

Currently, optimal treatment for chronic infection with HCV infection is a combination of therapy with pegylated interferon and ribavirin. Of haematological abnormalities that may be associated with such combination therapy, the most common is anemia[20]. Significant anemia (haemoglobin < 10 g/dL) has been observed in

9%-13% of patients receiving interferon and ribavirin; moderate anemia (hemoglobin < 11 g/dL) occurs in about 30% of patients undergoing such treatment[19,20,21].

There are several mechanisms by which anemia may occur during combination therapy for HCV infection, and ribavirin and/or interferons may contribute to anemia. In this context, hemoglobin concentrations decrease mainly as a result of ribavirin-induced hemolysis[19].

Anemia due to ribavirin leads to modifications of the dose in up to 25% of patients, and this type of anemia may be problematic in patients with HCV infection, especially those who also have renal or cardiovascular disorders. Adherence to ribavirin therapy is one factor that is critically important in the treatment of HCV infection. Although ribavirin-associated anemia can be reversed by reducing the dose of ribavirin or by discontinuing the drug altogether, this approach compromises outcomes by significantly decreasing rates of sustained virological response.

A recent study reviewed the predictors of anemia in patients undergoing treatment for HCV infection[20]. Patients with impaired renal function may be at an increased risk of ribavirin-related anemia and, accordingly, should be monitored carefully. Furthermore, a decrease in haemoglobin concentration of ≥ 1.5 g/dL by week 2 of treatment has been found to be an excellent early

predictor of subsequent substantial decreases in hemoglobin. This predictor might be applied to identify candidates for early intervention for management of anemia to facilitate maintenance of the dose of ribavirin. One of the specific approaches to manage ribavirin associated anemia is administration of recombinant human erythropoietin[20]. After 16 wk of ribavirin therapy, patients who had also been given erythropoietin alfa had significantly higher mean hemoglobin levels than patients in a control group. In patients with chronic hepatitis C, viramidine , a prodrug of ribavirin that is selectively taken up by the liver, has the potential of maintaining the antiviral efficacy of ribavirin, while decreasing the risk of haemolytic anemia[22].

Interferons may also contribute to anemia. Their main relevant action is induction of bone marrow suppression. This effect of interferon results in suppression of compensatory reticulocytosis associated with ribavirin induced haemolytic anemia. Thus, the bone-marrow suppressive effect of interferon may contribute to anemia, which complicates therapy with combination of interferon and ribavirin[22].

5. Alcohol, Liver Disease and Anaemia

Alcohol is implicated in the pathogenesis of chronic liver disease; it may contribute to anemia secondary to its direct effects on the liver and also to other diverse mechanisms (Figure 1)[23].

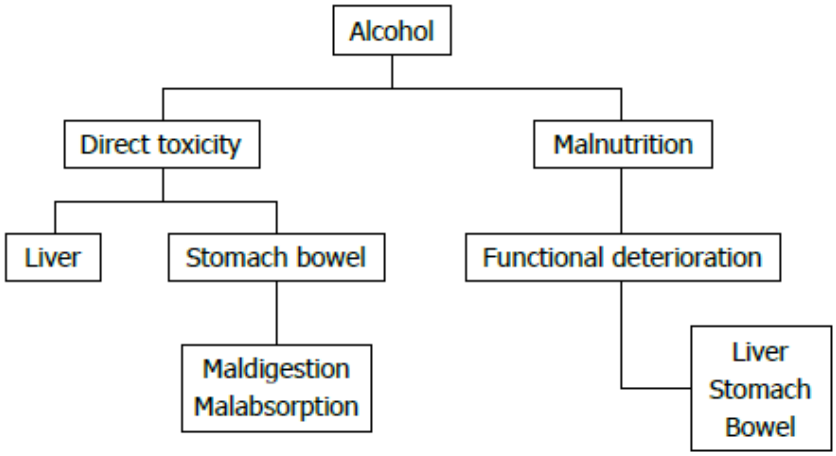


Figure 1 – Depicts how different attributes of alcohol contribute to anaemia (Moreno Otero et al[23])

Markers of iron overload tend to be higher among those who consume more than two alcoholic drinks per day than among non-drinkers, after adjusting for potential confounding factors[24]. Consumption of alcohol appears to be associated with an approximately 40% reduction in the risk of development of iron deficiency anemia. Folic acid and vitamin B12 deficiencies develop frequently in patients with cirrhosis. These deficiencies may be related to inadequate food intake or intestinal malabsorption. They are suspected when examination of a blood film reveals hypersegmented cells and oval macrocytes, in addition to round macrocytes characteristic of chronic liver disease. When anemia is caused by these deficiencies, the mean corpuscular volume is increased and bone marrow shows megaloblastic erythropoiesis.

Anemia due to folic acid deficiency may result, not only from a lack of folic acid in the diet, but also the weak antifolate action of ethanol. Folic acid deficiency is the most common cause of a low hematocrit in hospitalized patients who are alcoholics[25,26].

Parenterally administered vitamin B12 not only corrects anemia caused by vitamin B12 deficiency, but may also induce improvement in the peripheral neuropathy that are associated with this deficiency[23]. Supplements of vitamins A, B and C may be administered empirically to patients with advanced alcoholic disease.

Anemia in an alcoholic may also arise as a consequence of the direct toxic effects of alcohol on erythrocyte precursors in the bone marrow. Management of alcohol induced suppression of erythropoiesis includes abstinence from alcohol and a nutritious diet with appropriate supplements. Other factors that may contribute to anemia and a low hematocrit in alcoholic patients are given in Table 3.

Table 3 - Etiological factors that may contribute to anaemia associated with alcoholism (Lewis et al[26])

Cause of low hematocrit	Possible contributing factors
Hemorrhage and/or iron deficiency	Alcoholic gastritis
	Portal hypertension
	Peptic ulceration
Hemolysis	Chronic liver disease and/or cirrhosis
	Zieve syndrome
	Spur cell anemia of severe liver disease
Reduced erythropoiesis	Anemia of chronic disease
	Nutritional (e.g. folic acid deficiency)
	Sideroblastic anemia
	Alcohol toxicity
Hypersplenism	Portal hypertension
Hemodilution	Fluid retention of chronic liver disease
	Aggressive intravenous fluid therapy

6. Anaemia Secondary to Nutritional deficiencies

i) Iron Metabolism

Serum iron is bound to Beta globulin transferrin which is synthesized in liver. Total iron binding capacity largely depends on the transferrin concentration[27]. High total iron binding capacity indicates iron deficiency. Iron binding capacity is often lowered in patients with liver disease due to decreased synthesis of transferrin. Serum transferrin receptor level is a more reliable lab index of iron deficiency in patients with liver disease.

Iron deficiency is also associated with hemorrhage and hemolysis. Iron deficiency causes microcytic hypochromic anaemia. Low or normal

serum iron concentration with a low or normal total iron binding capacity is frequently found in uncomplicated cirrhosis. In alcohol induced liver diseases, alcohol has a toxic effect and suppresses the bone marrow[28,29] but it increases the iron absorption from the GIT. Hepatic inflammation and necrosis tend to increase serum ferritin. The rise in MCV which accompanies alcohol ingestion masks the iron deficiency.

ii) Vitamin B12 and Folic acid metabolism

Intrinsic factor is required for B_{12} absorption and there is significant enterohepatic circulation. Pernicious anaemia is associated with primary biliary cirrhosis[30,31]. Alcohol inhibits B_{12} absorption, elevated B_{12} binding capacity occurs in cirrhosis and hepatocellular carcinoma. Liver stores 5 -10 mg of vitamin B_{12} representing 50 – 90 % of body stores[32].

Liver stores of folic acid are sufficient for only 4 to 5 months[32,33]. Alcohol induced liver disease and poor nutrition results in disordered folate metabolism. Hepatic necrosis leads to increased release of folate from liver and leads to increased urinary excretion. Altered B12 and folate metabolism causes macrocytosis.

7. Anaemia secondary to hemolytic syndromes in liver disease

Red cell life span in reduced by about 50 % in cirrhotics with, the spleen as the major site of destruction. The hemolysis may be due to

1. Hypersplenism
2. Lipid abnormalities.
3. Hemolytic anaemia is also seen in Wilson's disease and in autoimmune hepatitis (Coombs positive)[33].
4. Intracorpuscular defects such as instability of pyruvate kinase enzyme in alcoholic liver disease leads to hemolysis.

Recticulocytosis is frequently seen in liver disease patients with hemolysis.

ABNORMALITIES OF RED CELL SHAPE

Microcytosis is due to Iron deficiency of various mechanisms in decompensated liver disease[34].

Macrocytosis is seen mostly in alcoholics [35,36]. The increase in MCV is due to

- Increase in RBC membrane cholesterol and phospholipid content.

- Recticulocytosis associated with hemorrhage and hemolysis.

- Abnormalities in B12 and Folic acid metabolism.

- Intrinsic abnormality in bone marrow erythropoiesis.

Target cells: bowel or saucer shaped thin macrocytes.It is seen in seen in most cases of hepato cellular failure and cholestatic jaundice. Raised bile acids inhibit LCAT. So the red cell membrane LCAT is

decreased resulting in loading of membrane with cholesterol and lecithin forms target cells [37]

Acanthocytosis: Seen in severe liver disease. It is a bad prognostic indicator. Where it is associated with hemolytic anaemia it is called as spur cell anaemia[38].

Echinocytes: Speculated red cells due to changes in HDL in Liver disease patients.

Table: 4 Abnormality of RBCs[39]

Abnormality	Primary liver disorders	Disease in other systems
Macrocytes	Many types of liver diseases	Megaloblastic anaemia, Hypothyroidism, cytotoxic drugs.
Targets cells	Many types of liver disease	Thalassaemia, Other haemoglobinopathies, Hyposplenism, e.g. SLE, celiac disease
Spherocytes	Zieve's syndrome	Hereditary spherocytosis, Autoimmune haemolytic anaemia, Burns
Echinocytes Acanthocytes	Severe chronic liver disease Very severe disease (especially alcoholic) (spur-cell anaemia)	Haemolytic anaemia Abetalipoproteinemia Anorexia nervosa / Malnutrition McLeod phenotype
Burr cells Fragmented cells (schistocytes)	Hepatorenal syndrome	Renal failure, Thoromobotic thromobocytopenic purpura, Microangiopathic haemolytic anaemia, DIC, HELLP syndrome, some haemoglobinopathies
Stomatocytes, Tear – drop, poikilocytes	Alcoholic cirrhosis	Alcoholism, Haemolytic anaemias Primary and secondary myelofibrosis
Nucleated red cells, punctuate basophilla	Acute fatty liver of pregnancy	Infections, e.g.malaria Heavy metal poisoning Haemolytic / dyserythropoietic anaemia.
Rouleaux, Auto agglutination Sickle cells		Myeloma / macroglobulinemia / lymphoma / Autoimmune haemolytic anaemia Sickle cell disease.

WBC CHANGES IN LIVER DISEASE

Leukocytosis can occur in response to associated infection, hemorrhage, hemolysis and malignancy. Eosinophilia in frequently seen in association with parasitic disease, hepatocellular carcinoma, hepatic vein thrombosis, drug induced and also in primary biliary cirrhosis.

Leucopenia seen in Liver disease patients is due to hypersplenism[40] or a toxic effect on bone marrow (alcohol). Neutrophil function is affected by disturbance in late maturation of granulocyte differentiation. Chemotaxis is inhibited. There is a low level of complement C_3.

Hypergamma globulinemia is a well recognized feature of cirrhosis. It is initiated by immunization with enteric organisms normally filtered by liver. IgG and IgA are markedly increased[41]. There is generalized immunological hyperactivity. Benign monoclonal gammopathy is associated with primary biliary cirrhosis.

Specific Immunoglobulins are

IgA – Alcoholic cirrhosis

IgM – Primary biliary cirrhosis

IgG – Auto Immune Hepatitis.

DISORDERS OF BLEEDING

PLATELET AND CLOTTING FACTORS IN LIVER DISEASE

The liver plays a central role in blood coagulation. Acute and chronic hepatocellular diseases are usually associated with defective blood coagulation due to a variety of different causes. These include: decreased hepatic synthesis of factors II, VII, IX and X; the presence of inhibitors of these factors; decreased clearance of activated coagulation factors; thrombocytopenia; impaired platelet function; hyperfibrinolysis; and disseminated intravascular coagulation[42,43].

The Clotting Factors :

Liver is the principal site of synthesis of all the coagulation protein with the exception of vWF and factor VIII C[44]. The proteins include - i) Vitamin K dependent factors – II, VII, IX & X

ii) Labile factor – V

iii) Contact factor XI & VII

iv) Fibrinogen and fibrin stabilizing factors.

A summary of the coagulation cascade is shown in figure 2 :

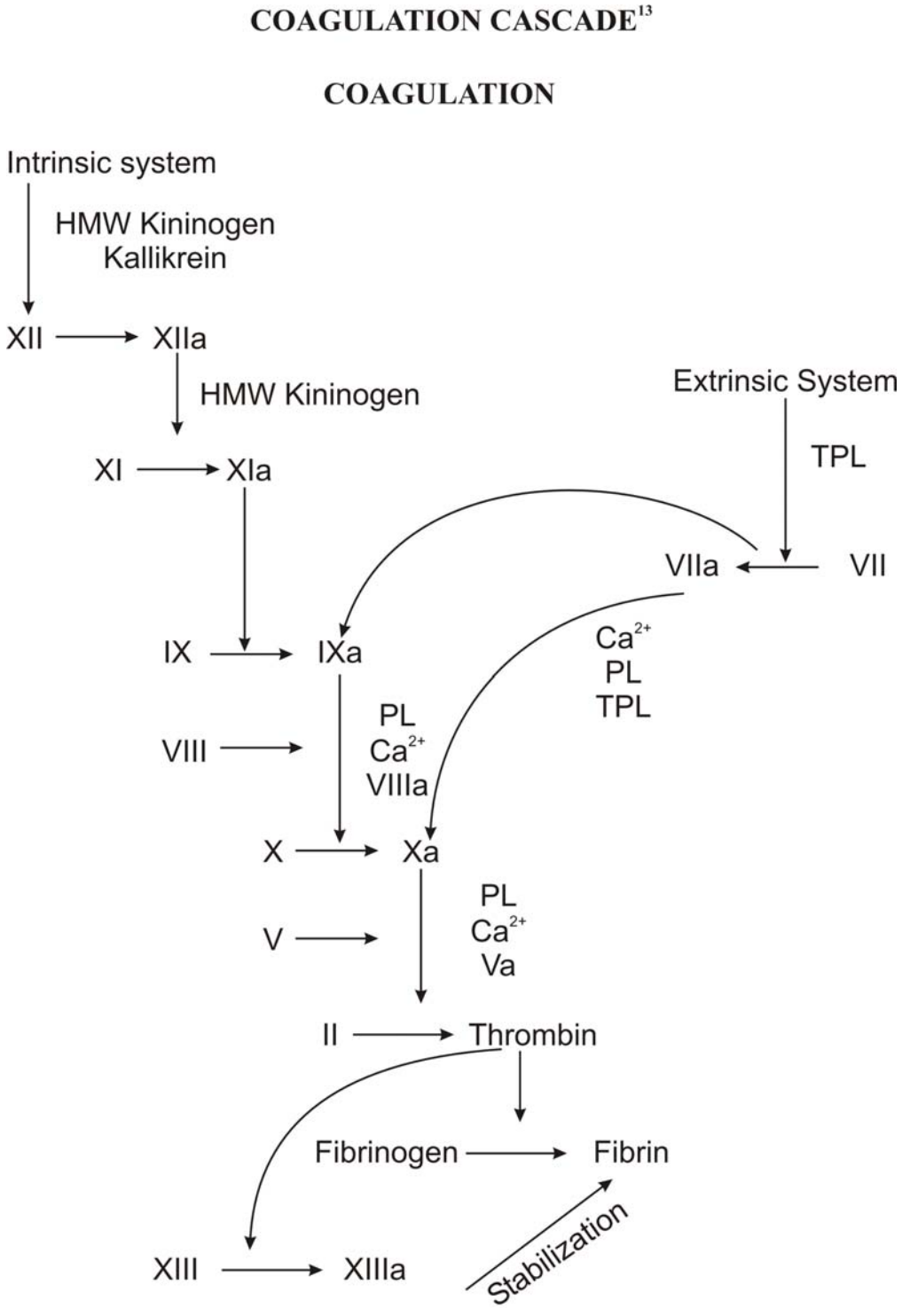


Figure 2 – Coagulation cascade.

Liver is the site of vitamin K storage. The Vitamin K is essential for the synthesis of factors II, VII, IX and X. The function of these blood clotting proteins depend on the conversion of glutamic acid residues, post ribosomally to γ carboxy glutamic acid by a carboxylase that requires vitamin K.

Factor VII is usually first to be decreased due to its short half life. The non functional precursor forms of clotting factors are called proteins induced in vitamin K. absence (PIVKA).They are produced with defective carboxylation in the presence of vitamin K deficiency.

Factor V is synthesized in liver in the absence of vitamin K. Thus a decreased level of factor V associated with decreased levels of factor II, VII, IX and X is an indicator of hepatocellular insufficiency. Hypofibrinogenemia is less frequent, until there is severe liver damage. Factors XI, XII and high molecular weight kininogen are usually moderately decreased. Prekallikrein decreases early in liver disease. Factor XIII, a fibrin stabilizing factor is also decreased.

An important coagulation defect associated with chronic liver disease is low levels of factor VIIa. In recent years, the hemostatic agent recombinant factor VIIa has become available as a potentially new therapeutic agent for use in the management of coagulopathy in patients with cirrhosis. This agent may enhance initial control of acute variceal bleeding[45]. However, such therapy is associated with significant side effects, such as vascular injury and thrombosis.

Functional abnormalities of fibrinogen molecule are known as dysfibrinogenemias. Acquired dysfibrinogenemias are most often associated with Decompensated Liver disease. Defective polymerization results from an abnormal glycosylation of fibrinogen molecules[46]. An increased level of sialyl transferase has been demonstrated in liver patients with dysfibrinogenemias[47]. Impairment in fibrin formation results in prolonged thrombin time. Abnormal type of prothrorombin due to defective carboxylation in des-γ -carboxy prothrorombin which is increased in chronic active hepatitis, cirrhosis and hepatocellular carcinoma.

Coagulation defects complicating liver disease predispose to an increased bleeding tendency, which increases both morbidity and mortality[42,43,48]. Defective blood coagulation associated with hepatocellular disease may be monitored using global screening tests, such as the PT and the activated partial thromboplastin time. In mild hepatocellular disease, PT usually is within the normal range or only modestly prolonged. In more advanced hepatocellular disease, prolongation of PT tends to reflect the severity of hepatocellular failure. Vitamin K routinely is administered parenterally (usually only once) to patients with liver disease and a prolonged PT, to exclude vitamin K deficiency as a cause of the prolonged PT[42].

Clotting Inhibitors :

Inhibitors of coagulation cascade are also synthesized by the liver. These are – Antithrombin III

Protein C & S (Vitamin K dependent)

Heparin cofactor II

Protein C, S , and antithrombin III are decreased in hepatocellular insufficiency[49]. The deficiency is not severe and usually parallels that of factor V. The synthesis is only affected by general damage to liver. Protein C deficiency parallels the deficiency of other vitamin K dependent factors. The level of protein S remains significantly greater due to extra hepatic source of protein S.

Although levels of naturally occurring inhibitors of blood clotting are decreased in hepatocellular insufficiency clinical evidence of thrombo embolism is rarely noted. This is probably due to the balance maintained between these inhibitors and the procoagulant.

Thrombocytopenia :

Thrombocytopenia (platelet count < 150 000/L) is common in patients with chronic liver disease; it has been reported in as many as 76% of patients with cirrhosis[22,43]. The pathogenesis of the thrombocytopenia is complex; it includes splenic pooling, and increased destruction and impaired production of platelets (Figure 3).

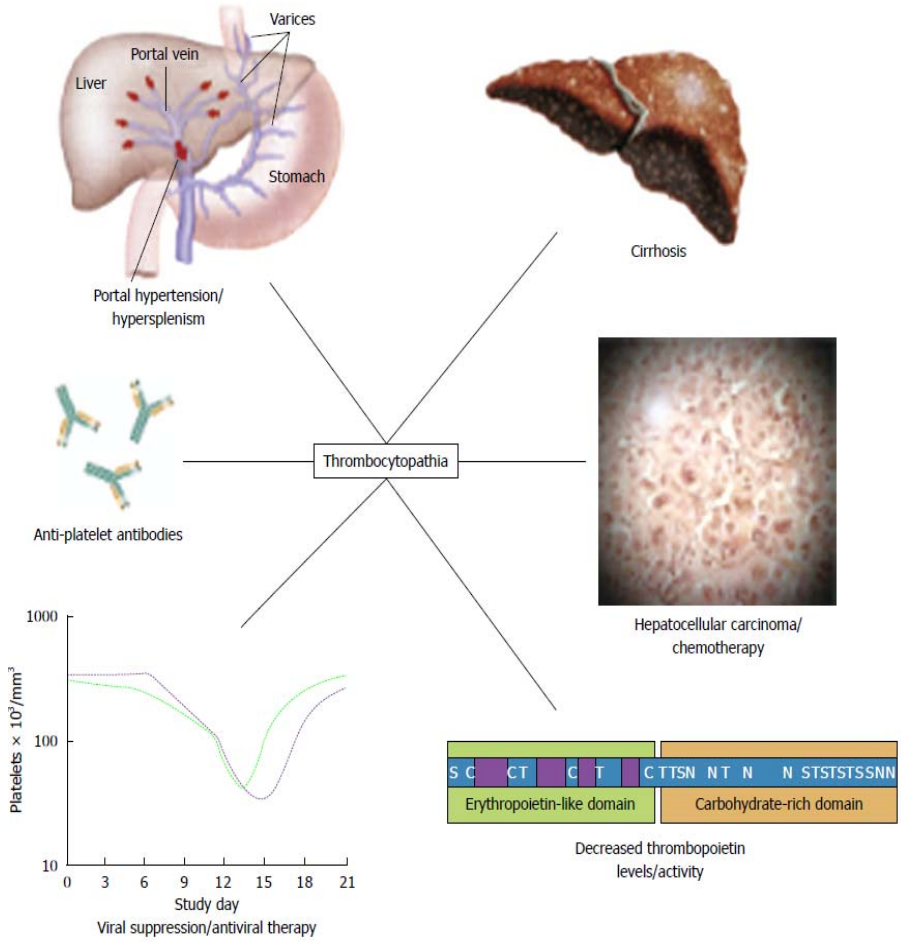


Figure 3 - Development of thrombocytopenia in patients with chronic liver disease (Afdhal et al[43])

Impaired production of platelets is caused, at least in part, by low levels of thrombopoietin. Prolonged bleeding time, and impaired aggregation, reduced adhesiveness and abnormal ultrastructure of platelets reflect abnormal platelet function; these abnormalities have been attributed to an intrinsic platelet defect. Specific treatments to attempt to reverse the effects of this defect

are not usually given, but platelet transfusions or platelet stimulating agents have been administered in some cases.

Hyperfibrinolysis :

Hyperfibrinolysis is another cause of impaired hemostasis in patients with liver disease. In decompensated liver disease patient, enhanced fibrinolysis is due to decreased hepatic synthesis of inhibitors α 2-antiplasmin and plasminogen activator inhibitor as well as decreased clearance of tissue type plasminogen activator.

In a nonrandomized trial[50], antifibrinolytic amino acids were administered to patients with acute or chronic liver disease, who had upper gastrointestinal bleeding and acquired defects of blood coagulation. However, administration of such amino acids does not have an established place in therapy.

Thrombosis and Disseminated Intravascular Coagulation (DIC) :

DIC is due to the consequence of non compensated formation of thrombin and leads to the formation of platelet thrombi and fibrin within the circulation. Thus it is associated with activation and consumption of circulating platelets and consumption of factors V, VIII, VII, II & XIII Protein C & S, antithrombin III, plasminogen and α plasmin inhibitor[51].

The release of tissue thromboplastin like material by necrotic liver had been the triggering factor for DIC in severe liver failure. Increased fibrinopeptide - A levels have been found in patients with cirrhosis and

chronic hepatitis. Elevated level of thrombin - anti thrombin complexes have been reported in chronic active hepatitis, decompensated liver disease, end stage liver disease and fulminant liver failure.

Thrombotic events, although rare in patients with cirrhosis, may occur. They tend to involve particularly the portal and/or mesenteric veins.

Summarising – Hemostasis in Liver Disease :

The abnormalities in hemostasis are due to

i. Impaired synthesis of clotting factors.

ii. Synthesis of abnormal clotting proteins.

iii. Quantitative, qualitative platelet defect

iv. Enhanced fibrinolytic activity

v. Disseminated intravascular coagulation[52].

A rational approach to managing disorders of blood coagulation in patients with liver disease is important because of the high risk of associated secondary hemorrhage.

PLASMA VOLUME

Plasma volume is frequently increased in patients with cirrhosis especially with ascites. Hypervolemia causes low peripheral hemoglobin or erythrocyte level[53].

The haemotological abnormalities discussed are summarized in the following Table-5 and Figure-4.

TABLE-5

COMBINATION OF HAEMATOLOGICAL ABNORMALITIES WITH[54] ABNORMAL LIVER FUNCTION TESTS

Abnormality	Haematological indices	Primary liver Disease	Disease in other systems
Red cell anaemia	Increased MCV (macrocytic)	Many liver diseases	Alcoholism, Vitamin B12/folate deficiency Haemolysis
	Low MCV/MCHC (microcytic)	With iron deficiency	Thalassaemia
	Normochromic Normocytic	With dilutional anaemia	Anaemia of chronic disease
	High reticulocyte count	With hypersplenism	Haemolysis Paroxysmal nocturnal haemoglobinuria
	Low reticulocyte count	With marrow aplasia (viral hepatitis)	
Normal haemoglobin Erythrocytosis	Increased MCV	Mild liver disease	Alcoholism
	Low MCV	With iron deficiency	Thalassaemia trait
		Hepatocellular carcinoma	
		Viral hepatitis (rare)	
White cells	Increased	With infection. neoplasia inflammation	Myeloproliferative disorder
	Neutrophils increased	With bacterial infection or steroid therapy	Leukemia, Lymphoma, drugs
	Lymphocytes increased	Viral infections	Connective tissue disorders
	Eosinophils increased	Parasitic infection	
		Drug hepatitis	
		Chronic active hepatitis (rare), sarcoidosis	
	Monocytes Basophils Mast cells increased		Tuberculosis, Leukemia, myeloprolifcrative disease
			Mastocytosis

Abnormality	Haematological indices	Primary liver Disease	Disease in other systems
	Decreased	With infection, marrow aplasia, or hyposplcnism	Infections (typhoid, SBE, tuberculosis, septicaemia) leukemia
	Lymphocytes		Viral infections
Platelets	Increased Decreased	Hemorrhage inflammation With hypersplenism. viral hepatitis	Myeloproliferativc disorder Leukaemia/lymphoma Connective tissue disorders Paroxysmal nocturnal haemoglobinuria

HAEMATOLOGICAL ABNORMALITIES IN DECOMPENSATED CHRONIC LIVER DISEASE[32]

The Haemotological abnormalities in chronic liver disease add morbidity to the primary pathology and increase the mortality. The possible factors are summarized in Figure 4.

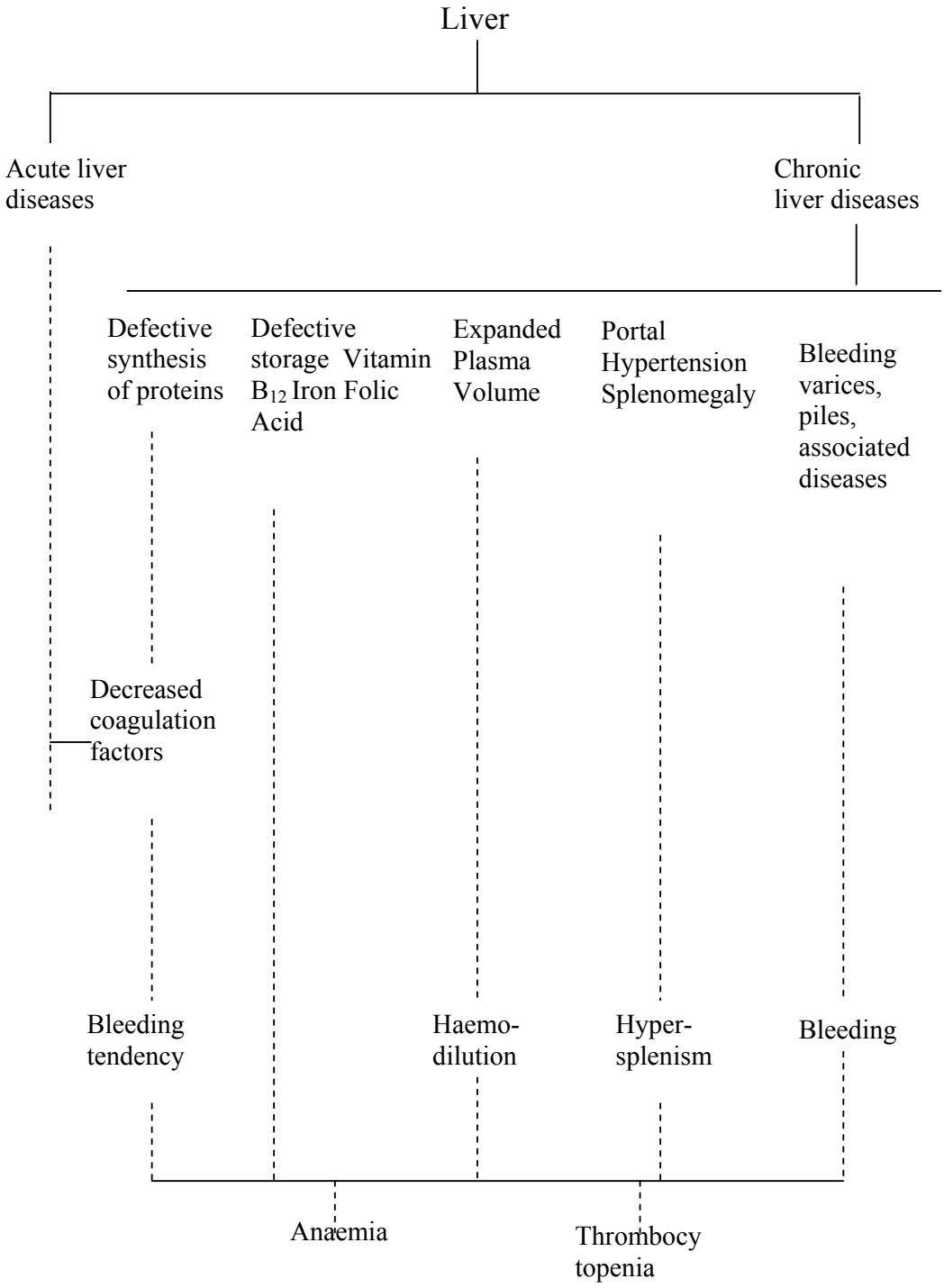

Liver
Acute liver diseases
Chronic liver diseases
Defective synthesis of proteins
Defective storage Vitamin B_{12} Iron Folic Acid
Expanded Plasma Volume
Portal Hypertension Splenomegaly
Bleeding varices, piles, associated diseases
Decreased coagulation factors
Bleeding tendency
Haemo-dilution
Hyper-splenism
Bleeding
Anaemia
Thrombocy topenia

Figure - 4

DESIGN OF STUDY

MATERIALS AND METHODS

To assess the prevalence of various hematological abnormalities in chronic liver disease, the study was conducted in Chengalpattu Medical College Hospital during the period from Sept 2010 to Nov 2010. A total 50 patients were selected in for this study.

All the cases included in the study were admitted in the hospital ward and were evaluated for chronic liver disease and the hematological abnormalities. Oral consent for the clinical examination and for the lab investigations were obtained from all patients. Written consent was obtained for bone marrow study.

All the patients were interrogated regarding their symptoms, like duration of illness, bleeding tendencies, abdominal distension, jaundice and oliguria and past history regarding previous treatment of diabetes, hypertension, tuberculosis, coronary heart disease, trauma, blood transfusion, surgery needle pricks and contact with blood products.

Personal history regarding alcoholism, smoking, high risk behavior and family history of any liver disease was also noted. Then the patient was subjected to general examination and systemic examination and were submitted to blood investigations.

Patients were diagnosed to have decompensated chronic liver disease by combined clinical and radiological workup. Clinical parameters included signs of liver failure whereas radiological parameters included proven hepatic cirrhosis with portal hypertension and splenomegaly by ultrasound.

After establishing the diagnosis patients were evaluated for hematological abnormalities. All blood investigations regarding hematological profile were done in clinical pathology laboratory in Chengalpattu Medical College Hospital. Bone Marrow aspiration was done in the medical wards under strict aseptic precautions.

Similarly prothrombin time and activated partial thromboplastin time were done at outside laboratory.

TO ASSESS RBC ABNORMALITY

1. RBC count :

RBC count was done with Neubauer's chamber using Hayem's fluid or auto analyser[44].

Normal Value:

1. Male 4- 5 to 5.9 x 10^6 mm^3

2. Female 4 to 5.2 x 10^6 mm^3

2. Hemoglobin estimation :

Done by Sahli's method, based on conversion of hemoglobin to acid hematin or acid analyzer.

Normal value:

1. Male 13.5 to 17.5 gm %

2. Female 12 to 16 gm %

3. Packed cell volume (PCV) :

It was done in autoanalyser or using microhematocrit capillary method.

Normal value:

1. Male 42 to 52 %

2. Female 37 to 47 %

4. **MCV, MCHC, MCH :**

Were estimated by autoanalyser

(I) MCV = $\frac{PCV x 10}{RBC \text{ in million per cumm}}$

80 – 97 FL – Normal

< 80- microcytic

>97 – macrocytic

(ii) MCH $= \frac{Hbx10}{RBC\ in\ million\ per\ cumm} (Pg)$

27 - 31 - Normal

< 27 – Hypo chromic

> 31 - Hyper chromic

(iii) MCHC $= \frac{Hbx100}{PCV} (\%)$

32 – 36 % - Normal

< 32 Hypo chromic

> 36 – Hyper chromic

5. Peripheral smear for blood picture :

Using Leishmann's stain blood picture was examined with a lab microscope.

(i) Low power field examination:

- Quality of film
- Number, distribution and staining of WBCs
- RBCs examination

(ii) High power field examination:

Assess RBC - Size, Shape, Hemoglobin concentration

(iii) Oil immersion examination:

Assess atypical cells and inclusion bodies

6. Reticulocyte count :

Stain - 1% brilliant cresyl blue

Normal – 0.2 – 2 %

7. Bone marrow study (not conducted in 23 patients because of hemostatic abnormalities[55,56].

II) To assess WBC abnormality :

1. Total WBC count

Done by QBC method or using Neubauer's chamber with Turke's fluid. Normal 4,500-11,000 cells per cmm[27]

2. Differential count

Assessed by QBC method or direct staining and visualizing with lab microscope.

III) To Assess hemostasis :

1. Platelet count

Manually was done by Rees Eecker method (staining with brilliant cresyl blue dye or by auto analyzer).

Normal 1.5 to 3.5 x 10^5 / mm^3

2. Prothrombin time :

Done by Quick one stage method. Normal (10 – 14 sec).

3. Bleeding time – By Ivy's method- Normal (1-7 mts)

4. Clotting time by lee & white method – Normal (5 -15 min)

5. Activated partial thromboplastin time Normal (24 – 34 sec).

IV. Liver function test :

In fifty cases, the following biochemical investigations were carried out to prove the presence and assess the severity of hepatocellular failure.

1. Serum Proteins — Total; Differential — Albumin, Globulin
2. Serum billirubin — Total; Differential — Conjugated, Unconjugated
3. Serum Alkaline phosphatase
4. AST and ALT.

INCLUSION CRITERIA

1. Adult patients presenting with signs and symptoms of chronic liver disease.
2. Liver function tests showing indication of liver disease
3. USG showing cirrhotic liver with portal hypertension and splenomegaly

EXCLUSION CRITERIA

1. Acute liver cell failure, as characterized by normal liver echotexture by USG
2. Patients with known GIT malignancy or known primary hepatocellular carcinoma.
3. Patients with primary coagulation disorder,
4. Liver cell failure due to infective cause like septicemia or end toxemia.

DATA ANALYSIS

This study regarding assessment of hematological profile and hemostasis was conducted among 50 inpatients in medicine department at Chengalpattu Medical College Hospital.

Age and Sex Distribution :

Out of 50 patients in this study, there were 40 male patients and 10 female patients. The age of patients in this study was in the range from 20 to 60 years as shown in Table-6, Figure-5 and Figure-6.

Table 6 – Age Distribution of the study group

Age	Percentage. of Cases	No.of Cases	Male	Female
20 to 30	6%	3	2	1
30 to 40	38%	19	15	4
40 to 50	40%	20	16	4
50 to 60	16%	8	7	1

Most of the patients in the study were in the middle age group and only 6% were in younger age. Out of 3 patients one patient was diagnosed to have Wilson's disease and others were of unknown etiology. Remaining 47 patients were diagnosed as chronic decompensated liver disease with pathology as cirrhosis and were of variable etiology.

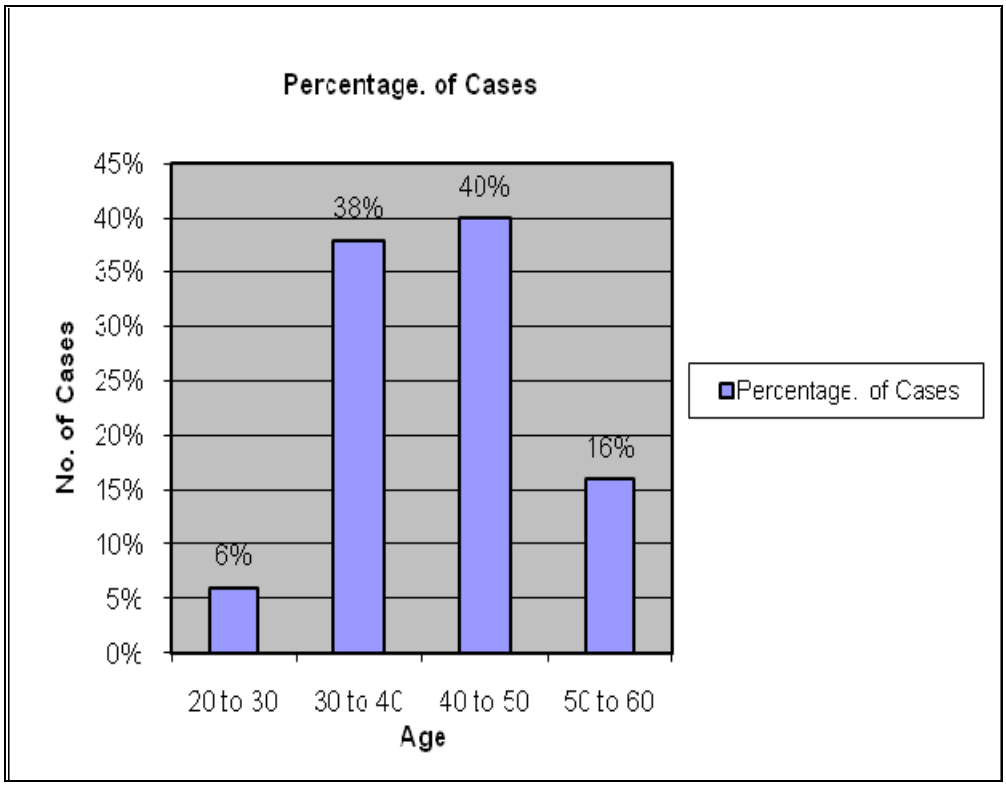


Figure -5

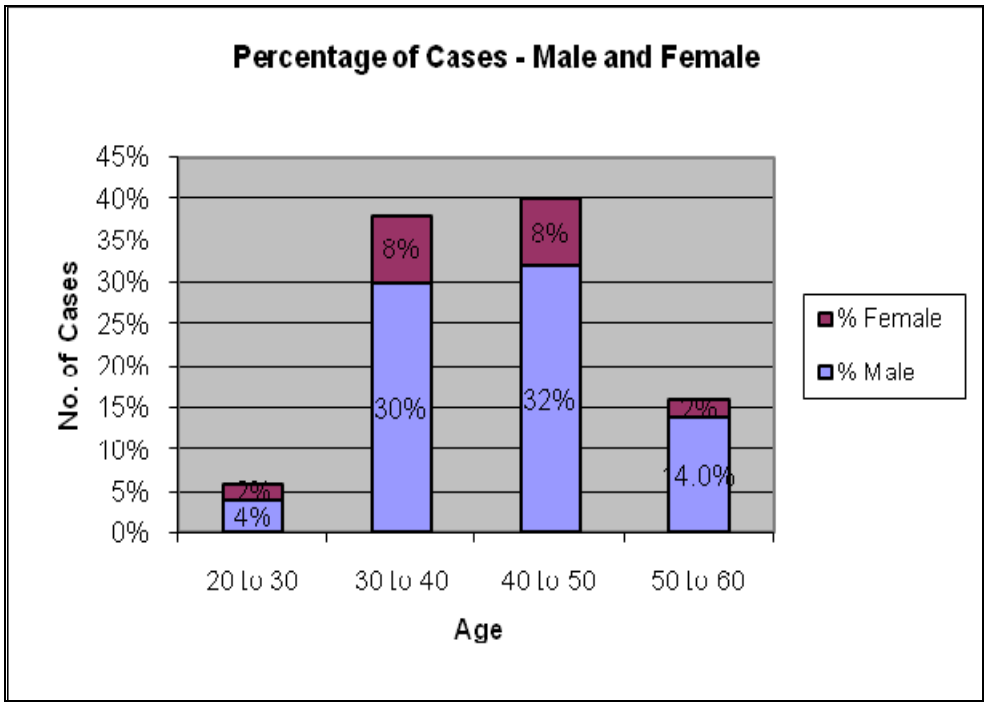


Figure - 6

PRESENTING HISTORY

ALCOHOLISM

Among 10 female patients, none gave history of alcoholism and among the 40 male patients 36 patients were found to be alcoholics.

HISTORY OF JAUNDICE

Among 50 patients only 25 patients had history of jaundice. Later serologic investigations for HBV Ag. Anti HCV antibody showed 6 patients positive for HBS Ag and only one shows positive for anti HCV antibody.

While coming to data analysis of investigations, among the 50 Chronic Liver Disease patient's only 43 patients has raised billirubin level. About 7% of the patients were with normal billirubin level.

TABLE – 7 - ANALYSIS OF SYMPTOMS

Symptoms	No.of Cases	Percentage of Cases
Weakness & Fatigue	37	74%
Anorexia	34	68%
Nausea / Vomiting	22	44%
Distention of abdomen	50	100%
Jaundice	25	50%
Bleeding Tendency	24	48%

Among the 50 patients 68 % had anorexia and 74 % had weakness and fatiguability. Jaundice was found in 50 %. Bleeding tendency was observed in 48 % of them.

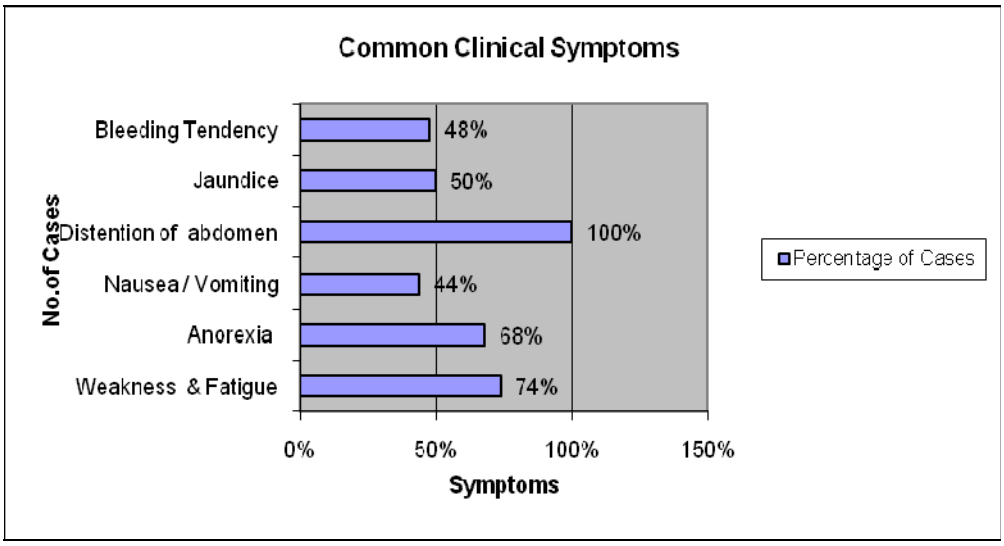


Figure 7 – Common Clinical Symptoms

CLINICAL EXAMINATION

Among the 50 patients, 50% had Jaundice and 54% had anemia. Splenomegaly was observed in 92%. Ascites was present in 100% of the patients.

Table – 8 and Figure – 8 summarises the clinical findings in the study group.

TABLE – 8 - ANALYSIS OF SIGNS:

No.	SIGNS	No. of cases	%
1	Anaemia	27	54%
2	Jaundice	25	50%
3	Pedal edema	33	66%
4	Spider angiomas	3	6%
5	Purpura & Bruises	3	6%
6	Gynaecomastia and Testicular atrophy	10	20%
7	Dilated veins over abdomen	18	36%
8	Splenomegaly	46	92%
9	Ascites	50	100%
10	Asterixis	4	8%

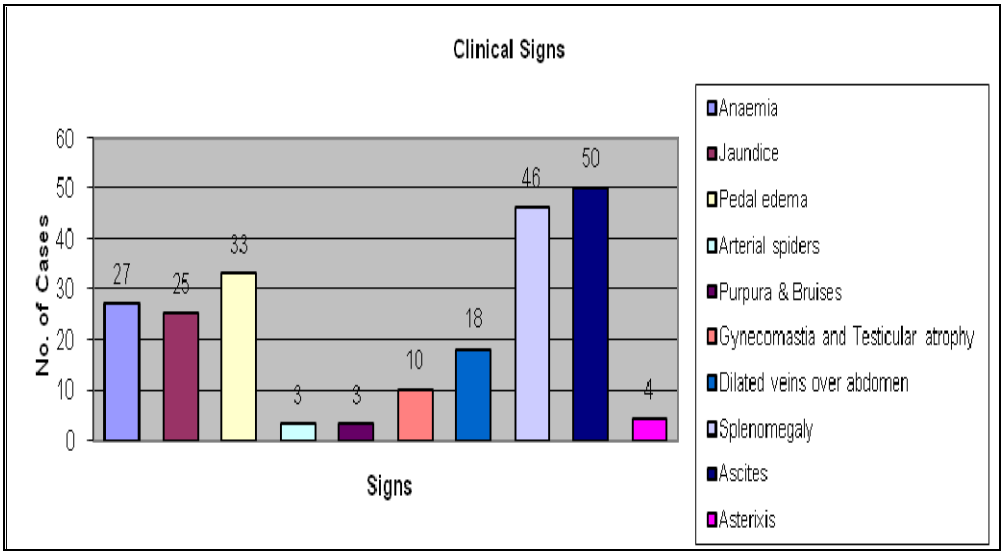


Figure – 8 – Analysis of Signs

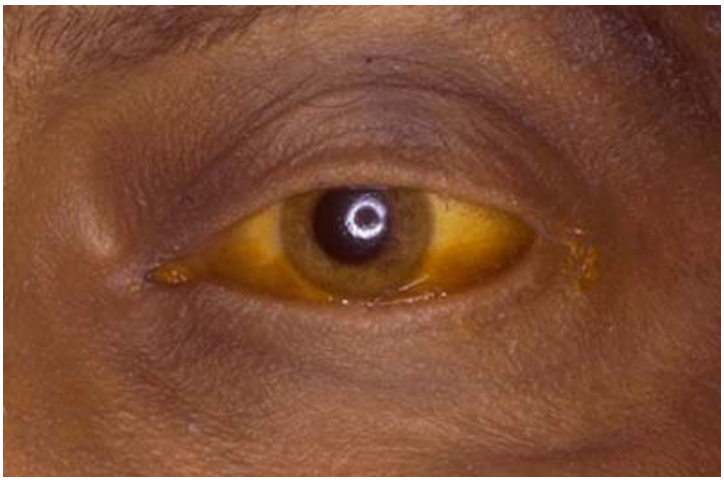


Fig. 9 Jaundice

ANALYSIS OF RBCS

Patients in the study were analysed for the presence and absence of anaemia and the characteristics of anaemia when present.

44 patients had anaemia and only six patients had normal hemoglobin above 12 gm%. About 14 patients had severe anaemia less than 8 gm%.

Table -9 - Anaemia in Chronic Liver Disease

Haemoglobin gm %	Cases	Percentage
< 6	2	4%
6 to 8	12	24%
8.1 to 10	22	44%
10.1 to 12	8	16%
12.1 to 14	6	12%
> 14	Nil	

Table 10 - RBC count in chronic liver disease

RBC Count	Cases	Percentage
2.5 to 3	8	16%
3 to 3.5	10	20%
3.5 to 4	17	34%
4 to 4.5	11	22%
> 4.5	4	8%

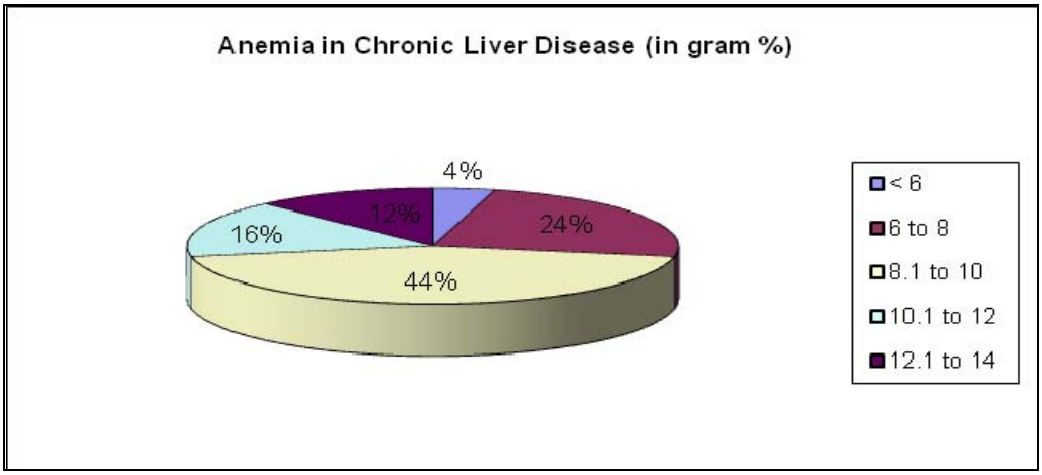


Figure - 10

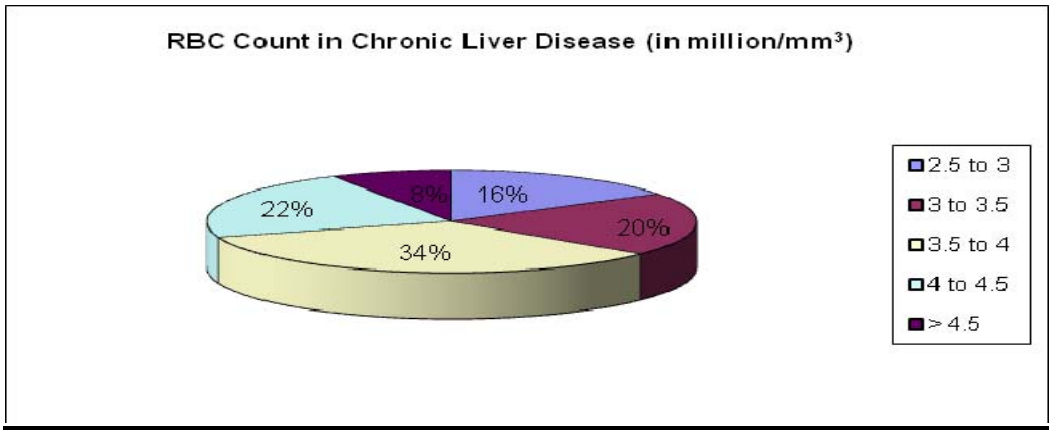


Figure - 11

CHARACTERISTICS OF ANAEMIA

All the 6 patients with normal hemoglobin level had normochromic and normocytic blood picture. Among the 44 patients with anaemia, 11 patients had normochromic and normocytic anaemia, 11 patients had microcytic anaemia and 11 patients had macrocytosis. Only one had dimorphic anaemia. Patients with microcytic anaemia showed anisocytosis and poikilocytosis**.**

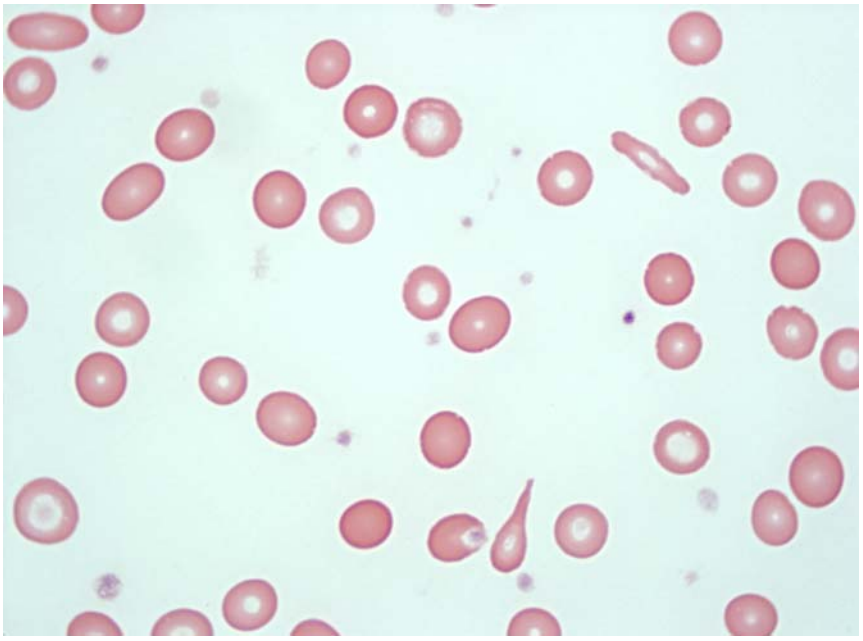
Target cells were seen in only six patients. **Acanthocytes** was not seen in any of the peripheral smears. Patients with macrocytosis had meant corpuscular volume more than 97 fl.

Table 11 - Type of Anaemia

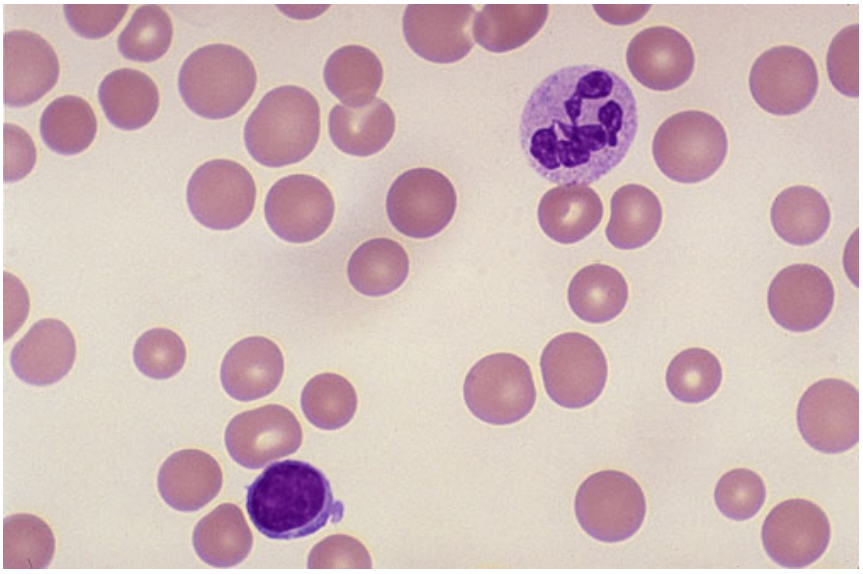
Type of RBCs	Patients with anaemia	Percentage
Normocytic	11	22 %
Microcytic	11	22 %
Macrocytic	11	22 %
Dimorphic	1	2 %

TYPE OF ANAEMIA

BLOOD PICTURE

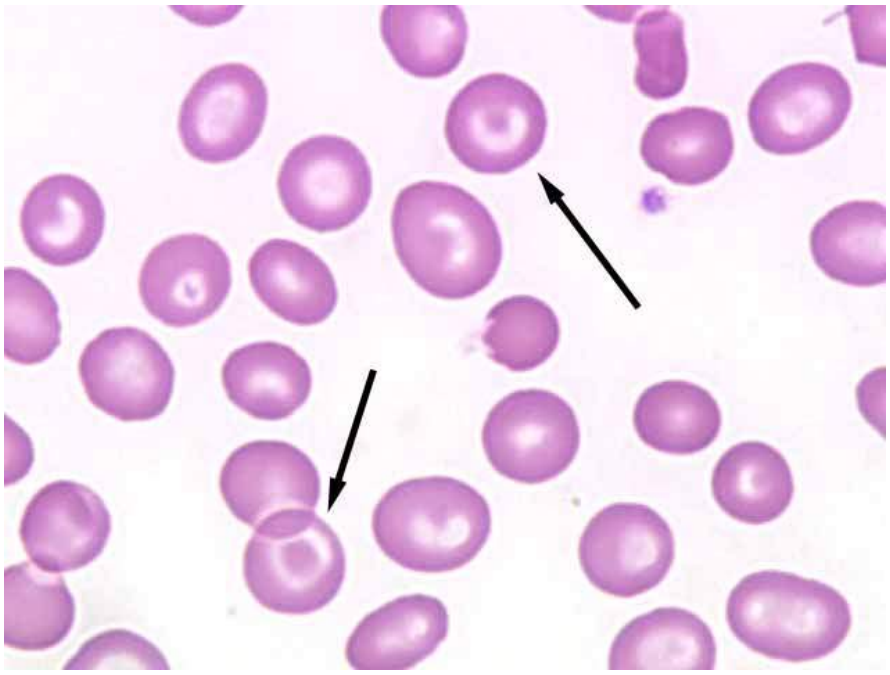


Microcytic Hypochromic Anaemia With Tear Drop Cell

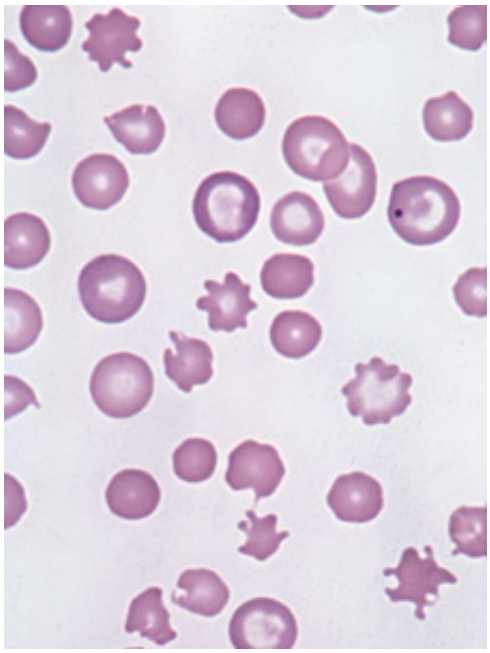


Macrocytosis with Hypersegmented Neutrophils

BLOOD PICTURE



Target Cells



Acanthocytes

WBC ABNORMALITIES

The analysis of WBCs was done with the total count and the differential count. The total count of WBCs range from 2700 / mm^3 to 17,000/mm^3.

Among the 50 patients Leukocytosis were observed in 11 patients. Eosinophilia was found in two patients. Leukocytosis were observed in patients with fever due to secondary infection of ascites due to repeated paracentesis and four patients had Leukocytosis due to spontaneous bacterial peritonitis. Leucopenia was present in 12% of patients. Lymphocytosis seen in 12 % of patients, Eosinophilia in 4 % of patients.

Table 12 - WBC COUNT IN CHRONIC LIVER DISEASE

Total count in Cells / mm^3	No. of patients	Percentage
< 3000	3	6%
3000 – 6000	8	16%
6000 – 9000	12	24%
9000 – 12000	16	32%
> 12, 000	11	22%

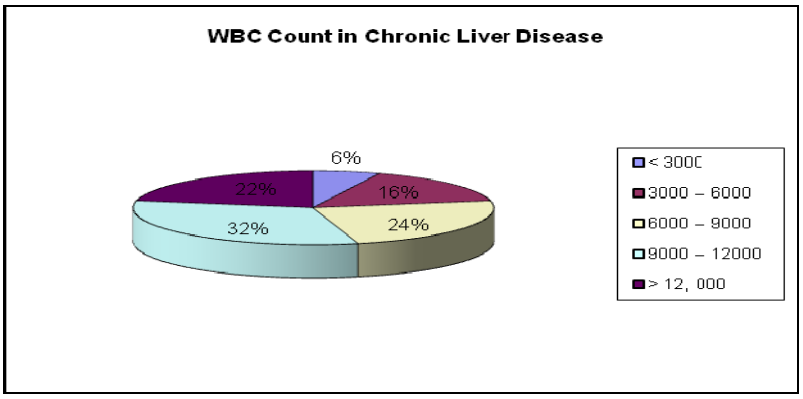


Figure 12 - WBC Count in Chronic Liver Disease

PLATELET ABNORMALITIES

Table 13 - Platelet Count in Chronic Liver Disease

Total count in Cells / mm^3	No. of patients	Percentage
< 50,000	4	8%
50,000 – 1,00,000	6	12%
1 – 1.5 Lakhs	13	26%
1.5 – 2 lakhs	14	28%
> 2 lakhs	13	26%

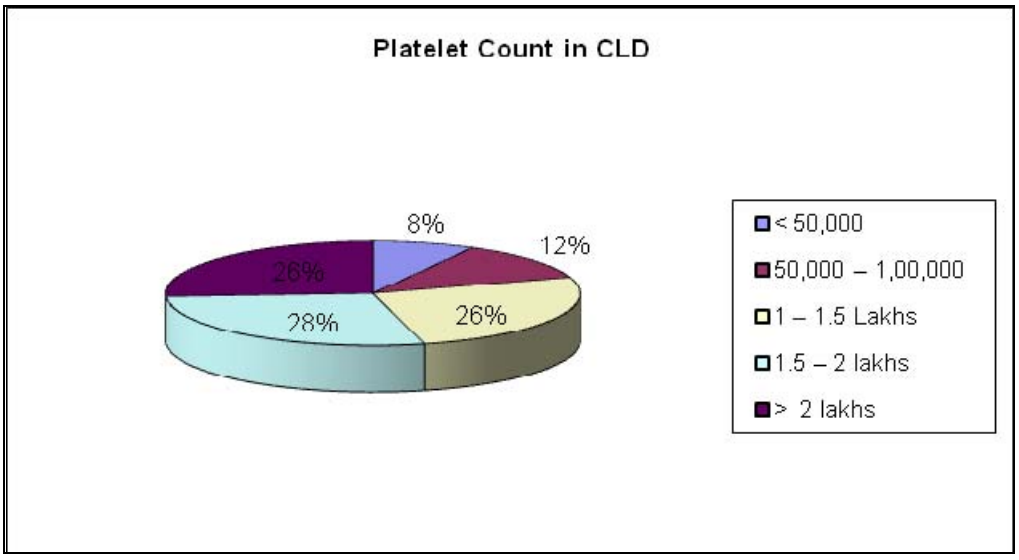


Figure 13 – Platelet Count in DCLD

Thrombocytopenia was found in 23 patients among 50 cases is the study. Severe thrombocytopenia of < 50,000 cell / mm^3 was found in patients with large spleen >8 cms and had a history of massive hemetemesis. Thrombocytopenia was associated with history of atleast

an episode of hematemesis. Among the patients with severe thrombocytopenia 3 patients were found to have disseminated intravascular coagulation, later confirmed by the raised value of APTT and PT.

Among the patients with normal level of platelets about 6 patients had history of atleast on episode of hematemesis. Among the 27 patients with normal platelet levels about 11 patients had mild Splenomegaly and 6 patients had moderate splenomegaly. In 5 patients Splenomegaly was observed in Ultra Sonogram only.

SERUM PROTEINS

Patients were analysed for the estimation of serum proteins, which is the synthetic function of the liver and evaluated for albumin globulin ratio which will be altered in the chronic liver disease patients.

Table 14 - Serum Proteins in Chronic Liver Disease

Total proteins gm%	No of patients	Percentage
>6	7	14%
6 to 5	22	44%
5 to 4	17	34%
<4	4	8%

Among patients only 14% had total proteins more than 6 gm% and four patients had total protein <4 gm% and others were in the middle group. 44% had protein in the range of 6-5 gm% and 34% had protein in the range of 5-4 gm% .

All the patients had albumin globulin ratio reversal, which again, favours the diagnosis of Chronic Liver Disease.

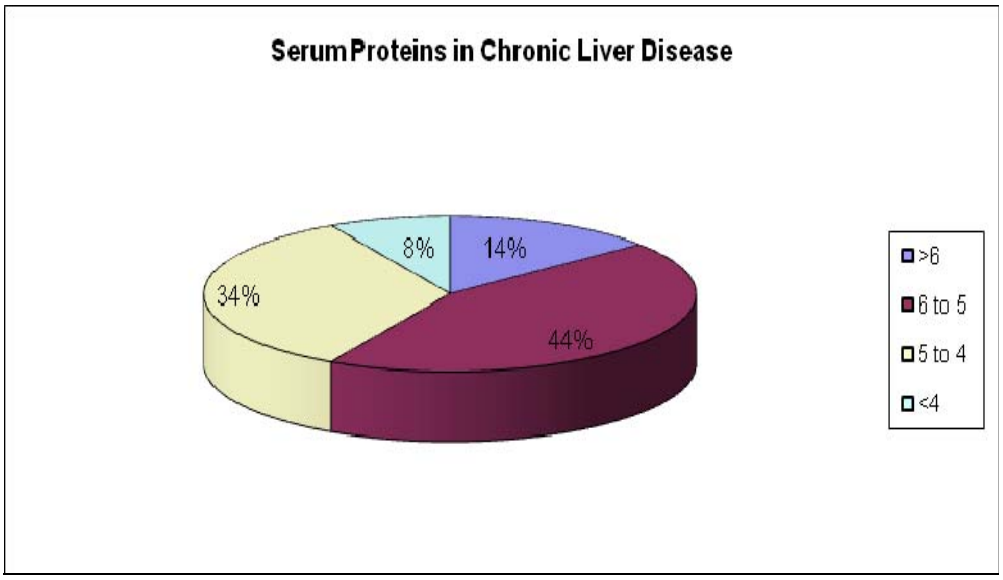


Figure - 14

ABNORMALITIES IN COAGULATION

The liver secretes all the clotting factors, except factor VIII and VWF. As we had no facility for the estimation of individual clotting factors, the patients were assessed for the coagulation profile by testing for prothrombin time and activated partial thromboplastin time. Among the 50 patients 20 patients had prolonged prothrombin time and 30

patients had normal prothrombin time. There was no correlation between the severity of jaundice and the prolongation of prothrombin time.

Among the 20 patients with prolonged prothrombin time about 8 patients had history of atleast one episode of hemetemesis.

Table 12 - Hemostatic Parameters

No	Type of change		No. of cases	%
1.	**Platelet Count**			
	Normal (>1.5 lakhs)		27	54 %
	Low normal (1-1.5 lakhs)		13	26 %
	low (< 1 lakhs)		10	20 %
2.	**Bleeding time**		35	70 %
	(1-7 mts)	Normal	35	70 %
		Prolonged	15	30 %
3	**Clotting time**			
	(<15 mts)	Normal	50	100 %
		Prolonged	0	0.0
4	**Prothrombin time**			
	(10-14 sec.)	Normal	30	60 %
		Prolonged	20	40 %
5.	**APTT (24-34 sec)**	Normal	48	96 %
		Prolonged	2	4 %

Bleeding time was prolonged in the 10 patients who had platelet counts less than 1,00,000 / mm^3 Bone marrow study was not done with the patients with low platelet count and prolonged prothrombin time due to the risk of increased bleeding.

Among the 50 patients, APTT was prolonged in 2 patients. It was significantly raised in patients with DIC. They had history of spontaneous bleeding with internal bleeding and signs of endotoxemia. Both the two had severe thrombocytopenia with platelets < 50,000 / mm^3

Bone marrow biopsy was done in all patients except those patients who had abnormal coagulation profile. Most of patients had normocellular bone marrow and 22% patients had hyper cellularity. There was no hypoplasia and aplastic changes.

DISCUSSION

The study involving 50 patients done at Chengalpattu Medical College Hospital has thrown light over the hematological abnormalities of decompensated chronic liver disease. The results of this study confirms with previous published reports.

RBC ABNORMALITIES

In the study we inferred that 88 % of the total patients had anemia and among them 14 % of cases had Hb < 8 gm %.

According to studies by McHutchison JG, Manns MP, Longo DL; definition and management of anemia in patients infected with hepatitis C virus in Liver Int 2006; 26: 389-398; Anaemia occurs in 75 % of patients with chronic liver disease.

Similar studies conducted by Kimber C, Deller DJ and Lander H[57]; The mechanism of anemia in Chronic Liver Disease, in 1965; and by Sheehy W and Berman A; Anaemia occurs in upto 75 % of patients with chronic liver disease. It is characteristically of moderate severity and is either normochromic normocytic or moderately macrocytic.

In our study 14 % patient had severe anemia less than eight gm per cent. In patients with cirrhosis , anaemia is mostly due to.

I. Portal Hypertension and variceal bleed

II. Hypersplenism secondary to splenomegaly in portal hypertension

III. Defective coagulation

IV. Effects of alcohol on bone marrow

V. Aplastic anaemia

VI. Treatment induced anaemia

VII. Decreased erythropoietin level as per the study Siciliano Hepatol 1995 who showed decreased erythropoietin level in cirrhosis patients with anemia when compared with patients with hypochromic anemia due to iron deficiency.

VIII. Chronic inflammation in cirrhosis suppresses the bone marrow.

Anaemia state is further worsened by accompanying

1. Bleeding esophageal and anorectic varies.
2. Bleeding peptic ulcer and gastropathy
3. Malignancy
4. Bleeding diathesis

In developing countries like India, people with poor socio economic state already will have nutritional anemia due to iron deficiency and B_{12} and folic acid deficiency, which is superimposed with cirrhosis leading to severe anemia. Female patients had a greater proportion of

severe anemia when compared with males. It shows the poor nutritional status of women in developing countries.

SERUM PROTEINS

As per Tavill AS study, fall in protein concentration usually reflect decreased hepatic synthesis[58]. In our study 100 % of cases had decreased albumin and total protein level and 90 % patients had albumin-globulin ratio reversal. The hypoproteinemia was also contributed by poor socio economic status of the patients who got admitted at the government hospitals.

The mechanism for the low albumin level in cirrhosis is due to decreased synthetic function of liver. In cirrhosis there is a chronic inflammatory[7] process in progression which causes elevated cytokines level such as IL-1, IL-6 and TNF-α which inhibits the synthesis of albumin and transferrin . About 10 gm of albumin is synthesized by normal liver, where as with cirrhosis, it synthesis only about 4 gms.

CHARACTERISTICS OF ANAEMIA

According to James Dooley, most common anemia seen in cirrhotic patients is normochromic and normocytic anemia[32].

In our study, interestingly, the prevalence of normocytic, normochromic anaemia was equal to that of microcytic and macrocytic anaemia. The incidence of normochromic normocytic anemia in our patients is 22 %. Where as in some studies there are varied results.

According to study done by Malhotra[59], 1951, the incidence of normocytic, normochromic anaemia was 90 %. In studies done by Bhatia (1961) and Mishra ET. al., (1982), the incidence were 59 % and 79 % respectively.

In some studies such as Kimber C. ET. al., reported 43 % of macrocytosis, which was supported also by the study by Bingham et al.

MACROCYTOSIS

The incidence of macrocytosis in our patients was 22%. Macrocytosis in cirrhosis is mostly due to the toxic effect of alcohol on RBC production in the bone marrow and deficiency of B_{12} and folic acid[60]. Folic acid deficiency is also exacerbated with alcohol[61] which was confirmed by the study done by Weir, Biochem, Pham 1985, and Lindenbaum[62].

MICROCYTOSIS

About 22% patients in our group had microcytic hypo chromic anemia. Bleeding, from esophagus and peptic ulceration or esophageal varies, compounded by the haemostatic defects of chronic liver disease, occurs in upto 70% of patients with Liver disease as per the study conducted by Kimber, Philips, et al. Microcytosis in cirrhosis is due to :

i. Decreased total iron concentration with alterations in iron metabolism due to decreased to serum transferrin.

ii. Hemolytic due to hypersplenism, autoimmune process, Lipid abnormalities or intra corpuscular defects.

The Total Iron binding capacity (TIBC) is often lowered in cirrhosis due to reduced hepatic synthesis of transferrin.

ABNORMALITIES OF WBCs

In our study group all the 50 patients WBC total count are in the range of 2700-17,000 cells per mm^3. About 11 patients had Leukocytosis which was mostly due to infections due to community acquired infections, nosocomial infection, spontaneous bacterial peritonitis and secondary peritonitis due to repeated peritoneal paracentesis.

In our study group in patients with Leukocytosis >12,000 / mm^3 of blood most of the patients had history of repeated hospital admissions and had repeated paracentesis. About 50 % of patients with Leukocytosis and high grade fever and all patients with Leukocytosis had increased cell count mostly of polymorphs in ascetic fluid analysis, which suggests the presence of peritonitis in this group of patients. Spontaneous bacterial peritonitis is one of the important causes of Leucocytosis[27].

Leucopenia present in 12 % of the patients may be due to

i. Direct influences of alcohol on bone marrow.

ii. Chronic inflammatory cytokines having suppressor effect on bone marrow.

iii. Hypersplenism

iv. Infection.

Eosinophilia is seen in association with parasitic disease and also associated with Hepatic vein thrombosis, hepatocellular carcinoma, and drug allergy and graft rejection. It is also found in primary biliary cirrhosis. Serum eosinophilia cationic protein is high in patients with primary biliary cirrhosis. Eosinophilia is present in 2% of cases in our study group mostly due to parasitic infection.

IMMUNOGLOBULINS AND LIVER DISEASE

As per the studies by Feizi Gut (1968) and Jensen, Arch Int Med., 1982[63] , it has been proved that hyperglobulinemia is a well recognized feature of cirrhosis. It has been suggested that this polyclonal hypergamaglobulinemia is initiated by immunization with enteric organisms normally filtered by the Liver.

Cirrhosis may be associated with a state of generalized immune hyperactivity, perhaps as a result of a defect of immune regulation. Peripheral blood mononuclear cells from cirrhosis with hypergamaglobulinemia had a normal proportion of B cells but that IgG and IgA hypergamaglobulinemia synthesis was markedly increased.

In our study almost all patients had hypergamaglobulinemia and 90 % of patients had albumin-globulin ratio reversal. The ratio reversal

is also contributed by lower albumin concentration due to decreased synthesis.

PLATELETS ABNORMALITIES

Defects of platelet number and function are well documented in patients with chronic liver disease contributing significantly to their hemostatic abnormalities. Alcoholic liver disease is associated with additional abnormalities which are probably a consequence of the toxic effect of alcohol on platelet production and function as proved by the studies by Mikhandes BMJ, 1986, Hilbom BMJ 1987[64].

Causes for thrombocytopenia are :

i. Shortened life span

ii. Platelet pooling in an enlarged spleen[65]

iii. Inability of bone marrow to compensate

iv. Reduced thrombopoietin level

In our study the above findings are evident and out of 50 patients 10 patients had thrombocytopenia < 1,00,000 / mm^3 and 13 patients had mild thrombocytopenia(1 – 1.5 lakhs / mm^3). All the patients with count less than one lakh had history of bleeding tendencies and among them two patients were diagnosed to have DIC, which also contributed to the very low platelet count in cirrhosis. All the patients with platelet count less than one lakh had increased bleeding time.

ABNORMALITIES IN HEMOSTASIS

Liver plays a major role in regulating hemostasis, synthesizing most of the clotting factors and coagulation inhibitors[66, 67], as well as some proteins of the fibrinolytic activated enzymes of the clotting and of the fibrinolytic system[68, 69].

The contributing factors are

1. Defective synthesis of coagulation factors
2. Thrombocytopenia
3. Increased fibrinolytic activity
4. Intravascular coagulation.

As per the studies Manner Ej, 1992 and Colman RW and Rubies R.N. blood coagulation 1988[70], clotting factors may be decreased even before any other evidence of liver damage[71, 72]. In hepatic cellular failure, factor VII is earliest to be decreased due to its short half life then followed by factors II and X. Factor IX is usually the last to be affected.

These vitamin K dependent clotting factors are synthesized in Liver. If their deficiencies are unresponsive to parenteral administration of vitamin K, it can be assumed that the hepatic synthesis of clotting factors is impaired.

PROTHROMBIN TIME ABNORMALITIES

In our study 20 patients had elevated prothrombin value which is evidence of clotting factor deficiency. They were treated with vitamin K injection for a period of one week and the prothrombin time was repeated. Some showed decrease in the prothrombin value

APTT ABNORMAILITY

APTT is prolonged in all coagulation defects including platelet activity and thromoboplastin. Prolonged APTT can be due to:

1. Vitamin K deficiency
2. Liver disease[46]
3. Presence of circulating anticoagulants.
4. Disseminated Intra vascular coagulation

In our study two patients had DIC and they had significant prolongation in APTT along with increased PT with severe thrombocytopenia. Other patients with history of bleeding tendencies were found to have moderately increased APTT.

According to James Dooley, APTT may be found to be moderate to highly prolonged according to the degree of liver failure[32]. In case of moderate deficiencies of factor II, IX, X and V, associated with a high level of factor VIII, APTT can be normal.[73]

DISSEMINATED INTRAVASCULAR COAGULATION

In our study 2 patients were found to have DIC and it was confirmed with prologation of PT and APTT along with severe thrombocytopenia and was confirmed by estimation of D-dimer. These patients were found to have septicemia, and they had blood culture positivity for gram negative organisms.

SUMMARY

Thus with the above studies we can infer that many of the haematological abnormalities noticed in decompensated chronic liver disease patients, contribute to the co-morbidity, which may in turn, reduce overall mortality.

From the above study we noted that the presence of severe anemia does not correlate with severity of disease as evident by normal serum billirubin and hypoalbuminemia. Instead it is related with history of bleeding tendency.

The character of anemia depends upon the various factors such as bleeding tendencies, dietary deficiency and alcoholism, but normochromic normocytic anemia is more common as per literature, and is mostly due to the hemodilution, blood loss and chronic inflammation suppressing the bone marrow. The Leukocytosis is associated with infections, mostly, secondary peritonitis due to repeated paracentesis and spontaneous bacterial peritonitis.

Platelet abnormalities as assessed by thrombocytopenia and increased bleeding time had no correlation with the severity of liver cell failure, but found to be best associated with patients with large spleen and more common in patients with bleeding tendencies.

Similarly prothrombin time and APTT are prolonged. This is correlated with the liver disease and there is significant rise in APTT along with severe thrombocytopenia in patients with DIC.

SUMMARY

50 patients of decompensated chronic liver disease were studied.

1. Almost 88% of the patients had anemia in any one of the form.
2. There was an equal distribution of normochromic normocytic, macrocytic and microcytic anaemia as inferred from the study.
3. Microcytic anaemia is found in 22% of studied population
4. Macrocytosis (22%) is almost common with alcoholics.
5. Abnormal red cells such as microcytic, microcytic, target cells, anisocytosis are found to be common in cirrhosis.
6. Leucopenia is found in 12 % of the study group. Leukocytosis is more common in patients with spontaneous bacterial peritonitis and secondary peritonitis.
7. Thrombocytopenia is present in 23% of patients and is commonly present in the patients with Splenomegaly and with the history of bleeding tendencies.
8. Prothrombin time prolonged in 40% of the patients. A significant rise in APTT with severe thrombocytopenia is found is DIC patients.

CONCLUSION

1. There is an equal prevalence of normochromic normocytic, microcytic and macrocytic anaemia. Microcytosis occur in patients with bleeding tendencies and macrocytosis occurs mostly in alcoholics.

2. Leucopenia occurs in a small fraction of patients and Leukocytosis occurs in patients with history of repeated paracentesis and peritonitis. Eosinophilia is associated with parasitic infections.

3. Thrombocytopenia is present in most of the cirrhosis patients and is associated with increased bleeding tendencies.

4. Increased prothrombin time and APTT occurs due to decreased synthesis of clotting factors.

5. All the cirrhosis patients must be evaluated for hematological and haemostatic abnormalities. Early treatment to correct these co-morbidities can decrease the overall mortality.

S.No.	Age	Sex	IP No.	COMPLETE HAEMOGRAM									Peripheral smear	Bone marrow	Hemostatic Parameters				LFT										
				RBC Count Mil/mm^3	Hb in gram %	PCV %	MCV in fl	MCH in pg	MCHC in %	TC mm^3	DC	Platelet			BT in min	CT in min	Pro thrombin time (sec)	APTT (Seconds)	Sr. Protein (gm%) T	A	G	Sr. Billirubin (mgm%) T	C	U	AST (IU)	ALT (IU)	SAP (IU)		
1	38	M	26172	4.1	9.3	30	74.6	20.4	27.3	6900	P65L33E1M1	Normal	microcytic Hypochromic	Normal	4	6	11	23	4.9	2.4	2.5	1.1	0.4	0.7	90	66	41		
2	45	M	26265	3.6	8.8	34.0	89.3	29.5	33.0	8400	P63L37E0	Low Normal	Normocytic Normochromic	Normal study	5'45	5'30	13	21	5.2	2.1	3.1	3.6	2.2	1.4	46	38	79		
3	39	M	26360	3.0	8.2	33	75.4	23.3	31.0	9300	P70L30E30	Normal	microcytic Hypochromic	Macronormo blast	4	6	11	23	5.6	2.8	2.8	4.8	3	1.8	102	89	86		
4	47	M	27200	2.6	5.5	27.0	77	24.0	31.0	14800	P50L46E4	Mod	Microcytic Hypochromic	Not done	8'3	5	17	23	5.9	3	2.9	3.2	2.6	0.6	69	97	80		
5	35	M	27274	2.8	6.7	33	101.0	34.0	34.7	6600	P67L30E3	Normal	macrocytosis Target cells	Not done	4'30	6'45	17	21	5.0	2.1	2.9	4.6	3	1.6	97	102	98		
6	39	F	27512	3.4	8.7	33.0	83	24.1	30.0	9300	P62L36E1M1	Mod	Normocytic Hypochromic	Not done	4	6'15	11	24	4.2	2	2.2	2.6	1.9	0.7	63	43	73		
7	59	M	29273	4.3	9.9	33	108.6	30.6	27.8	12500	P65L32E2	Normal	macrocytosis Target cells	Erythroid Hyperplasia	6' 15	8	15	22	4.9	2.4	2.5	5.1	3.1	2	78	67	94		
8	34	M	29861	3.9	8.9	36.0	73	22.0	30.0	3600	P49L46E4	Normal	Hypochromic microcytic	Normal study	4'30	6	12	22	5.8	2.8	3.0	3.6	2.4	1.2	87	73	76		
9	39	M	30165	5.0	12.1	39	101.0	32.0	32.5	9600	P58L39E3	Normal	Hypochromic microcytic	Not done	12	9	16	24	4.8	2.3	2.5	2.4	1.4	1	37	46	68		
10	55	M	30661	3.5	8.5	34.0	88.7	29.8	35.2	9300	P72L26E2	Normal	Dimorphic anemia	Micro nomoblast	5	6	13	25	6.2	3	3.1	2.1	1.7	0.4	20	34	91		
11	48	F	31195	3.9	8.2	40	79.1	25.0	31.2	6800	P55L43E2	Normal	Normocytic Hypochromic	Macronormo blast	4'15	4	13	26	5.1	2.1	3.0	2.4	1.8	0.6	63	47	48		
12	51	M	31555	3.5	8.1	32.0	76	26.0	35.0	12300	P72L28E0	Low Normal	Hypochromic microcytic	Not done	4'30	6	11	23	5.2	2.5	2.7	2.4	1.2	1.2	22	24	88		
13	38	F	33421	2.9	7.1	29	111.0	34.0	31.3	10200	P65L32E2	Normal	macrocytosis Target cells	Not done	6	6'15	16	26	4.9	2.4	2.5	1.8	1	0.8	43	33	81		
14	36	M	33562	3.9	8.9	30.0	113.8	36.7	32.0	9300	P55L43E2	Normal	macrocytosis Target cells	Not done	4	6	11	23	5.5	2.7	2.8	2	1.2	0.8	36	38	88		
15	56	M	34173	5.0	12.1	34	76.6	25.3	33.2	4600	P52L36E2	moderate	Normocytic Hypochromic	Normal	4'30	6	15	21	4.5	2	2.5	5.2	3.2	2	78	89	92		
16	42	M	34192	4	11.5	32.0	102	29.6	28.6	3600	P50L46E4	Mod	macrocytosis	Normal	5'30	6	12	25	6	3	3.0	1.4	1	0.4	68	46	79		
17	37	M	34747	3.9	11.1	19	105.0	27.8	36.5	2700	P49L45E4M2	Normal	macrocytosis Target cells	Normal	6'30	8	12	23	4.9	2.4	2.5	1.2	0.5	0.7	38	41	48		

S.No.	Age	Sex	IP No.	COMPLETE HAEMOGRAM									Peripheral smear	Bone marrow	Hemostatic Parameters				LFT								
				RBC Count Mil/mm^3	Hb in gram %	PCV %	MCV in fl	MCH in pg	MCHC in %	TC mm^3	DC	Platelet			BT in min	CT in min	Pro thrombin time (sec)	APTT (Seconds)	Sr. Protein (gm%) T	A	G	Sr. Billirubin (mgm%) T	C	U	AST (IU)	ALT (IU)	SAP (IU)
18	36	M	35036	3.4	8.0	33.0	120	39.0	33.0	9200	P54L44E2	Mod	macrocytosis	Not done	5	4	13	27	4	1.8	2.2	4.6	3	1.6	92	69	67
19	29	M	35104	4.2	8.9	44	88.6	26.0	28.2	15200	P78L21E1	Normal	Normocytic Hypochromic	Normal	7	7'30	15	28	4	1.9	2.1	4.9	3	1.9	79	74	74
20	36	F	35196	2.7	7.3	31.0	104.4	32.3	31.3	2900	P50L46E4	Mod	macrocytosis	Not done	8'15	6	13	23	4.9	2	2.9	1.8	1	0.8	48	46	50
21	35	F	35229	4.0	9.1	38	91.2	30.7	34.0	6050	P48L36E10M6	Normal	Normocytic Normochromic	Not done	6'30	5	11	21	3.4	1.7	1.7	3.1	2.3	0.8	69	84	76
22	33	M	36644	3.4	7.7	33.0	79	24.0	30.3	8600	P62L36E2	Mod	Normocytic Hypochromic	Not done	8'30	6'30	14	28	4.2	1.6	2.6	3.2	2	1.2	61	47	94
23	35	M	36695	4.0	11.9	42	81.3	26.8	33.1	9300	P72L26E2	Normal	Normocytic Normochromic	Normal	9'0	5'3	17	27	6.1	3	3.1	2.6	2	0.6	77	71	48
24	36	M	36738	3.3	7.5	34.0	85.6	25.3	29.7	8600	P60L38E2	Normal	Normocytic Normochromic	Not done	12'15	9	20	35	5.2	2.1	3.1	3.4	2	1.4	40	32	78
25	46	M	37193	3.8	9.1	31	81.0	22.0	27.1	7200	P54L44E2	Normal	Normocytic Hypochromic	Not done	6'30	6	13	28	3.7	1.8	1.9	4.9	2.9	2	92	69	66
26	37	M	37205	3.9	9.5	33.0	115.2	38.8	34.1	12800	P78L21E1	Mod	Macrocytosis	Not done	8'3	5'30	11	24	5.6	2.7	2.9	1.6	0.8	0.8	96	67	109
27	48	F	37443	3.1	8.8	31	75.0	21.2	28.0	12200	P72L28E2	Normal	Microcytic Hypochromic	Normal	5'30	8	14	23	5.8	3	2.8	2.9	2.1	0.8	63	37	75
28	46	M	38197	3.5	7.6	31.0	87.6	27.6	31.7	6650	P54L43E3	Low Normal	Normocytic Normochromic	Not done	8	5'30	18	24	6	3	3.0	1.6	1	0.6	61	46	86
29	39	M	38240	3.8	9.0	36	73.0	22.0	30.2	5600	P45L46E3M1	Normal	Microcytic Hypochromic	Not done	6'30	6'30	12	24	5.1	2	3.1	2.8	1.9	0.9	38	32	46
30	47	M	38348	3.6	7.5	44.0	88.6	26.1	29.0	3400	P45L46E3M1	Mod	Normocytic Normochromic	Not done	4	6'15	13	26	4	1.9	2.1	3.2	2	1.2	69	87	63
31	49	F	39161	3.3	9.9	34	88.0	29.2	32.0	9200	P62L34E4	Normal	Normocytic Normochromic	Macronormo blast	3'30	7	14	26	5.7	2.7	3.0	1.9	1.2	0.7	43	33	67
32	49	M	39198	3.3	8.0	33.0	101	26.1	29.0	6700	P55L39E3	Low Normal	Macrocytosis	Not done	6	6'15	14	24	4.9	2.4	2.5	1.1	0.3	0.8	56	52	42
33	45	M	40085	3.6	10.2	38	85.4	25.4	29.2	5300	P40L46E14	Low Normal	Normocytic Hypochromic	Macronormo blast	4	7	15	28	6	3	3.0	1.2.	0.8	0.4	56	52	69
34	55	F	40176	2.5	7.6	35.0	93	24.5	26.2	14000	P65L32E2	Low Normal	Normocytic Normochromic	Not done	8'30	5'15	12	25	5.8	3	2.8	3.6	2	1.6	53	27	76

S.No.	Age	Sex	IP No.	COMPLETE HAEMOGRAM									Peripheral smear	Bone marrow	Hemostatic Parameters				LFT								
				RBC Count Mil/mm^3	Hb in gram %	PCV %	MCV in fl	MCH in pg	MCHC in %	TC mm^3	DC	Platelet			BT in min	CT in min	Pro thrombin time (sec)	APTT (Seconds)	Sr. Protein (gm%) T	A	G	Sr. Billirubin (mgm%) T	C	U	AST (IU)	ALT (IU)	SAP (IU)
35	42	M	40244	3.4	10.0	44	88.7	26.0	29.3	13500	P65L32E2	Low Normal	Normocytic Normochromic	Macronormo blasts	10'30	5	19	33	5.8	2.9	2.9	1.9	1	0.9	60	40	78
36	42	M	40286	3.1	8.0	34.0	88	29.5	31.0	12100	P46L46M4E2	Low Normal	Normocytic Normochromic	Not done	4'30	5	14	30	6.3	3.1	3.2	2.8	1.7	1.1	52	34	98
37	55	M	40445	2.5	7.6	34	93.5	23.0	24.4	9200	P62L36E1M1	Normal	Normocytic Normochromic	Macronormo blasts	4	5'30	11	27	5.3	2.2	3.1	2.4	1.9	0.5	29	27	84
38	40	F	40650	3.6	10.0	31.0	77.6	26.1	33.6	9800	P70L28E2	Normal	Microcytic Hypochromic	Not done	8'15	6	16	24	5.2	2.5	2.7	2.4	1.8	0.6	61	47	74
39	42	M	41277	4.8	13.7	39	89.3	28.6	32.3	7200	P52L38E0	Low Normal	Normocytic Normochromic	Normal	8'3	8	17	26	6.1	3	3.1	3	3	0.4	29	38	46
40	51	M	41445	2.4	5.9	29.0	76	24.2	31.7	9400	P58L40E2	Mod	Microcytic Hypochromic	Not done	8	6'45	14	26	4	2	2.0	2.4	1.2	1.2	62	47	66
41	47	M	43377	4.2	12.0	22	76.0	26.7	35.2	9000	P58L39E3	Low Normal	microcytic Hypochromic	Micro normo blast	5	6'30	14	25	5.7	2.8	2.9	1.2	0.8	0.4	37	46	66
42	38	M	43465	4.0	10.1	37	85.0	26.6	30.2	12100	P72L28E0	Normal	Normocytic Normochromic	Erythroid Hyperplasia	5'45	5	17	23	5.4	2.5	2.9	3.2	2	1.2	30	22	62
43	33	M	43637	4.4	12.3	37	87.1	26.4	30.0	5900	P40L46E14	Low Normal	Normocytic Hypochromic	Normal	5'15	7'30	11	21	4.9	3	1.9	3.1	2.7	0.4	87	73	102
44	27	F	43677	2.7	10.1	34	79.0	26.2	33.1	9300	P58L40E2	Normal	Normocytic Hypochromic	Normal	6'45	9	16	21	5.9	2.9	3.0	3.2	2.2	1	29	33	59
45	41	M	43778	4.4	12.1	34	88.7	29.2	32.7	9300	P72L25E0	Normal	Normocytic Normochromic	Normal	3'45	9'30	14	21	5.9	2	2.9	2.1	1	1.1	36	33	76
46	48	M	43982	3.8	9.6	33	88.0	30.6	28.1	2900	P49L45E4M2	Normal	Normocytic Normochromic	Normal	3'30	4	17	23	4.2	2	2.2	3.4	2.6	0.8	66	59	85
47	45	M	44498	5.0	13.3	34	93.0	23.0	24.2	6900	P58L40E2	Low Normal	Normocytic Hypochromic	Normal	9'30	7'30	16	27	3.7	1.7	2.0	4.8	2.8	2	92	70	92
48	23	M	44577	3.8	9.9	37	86.2	24.0	27.9	5700	P45L46E5M1	Normal	Normocytic Hypochromic	Erythroid Hyperplasia	5	6	14	25	3.8	1.8	2.0	2.2	1.5	0.7	74	59	75
49	53	M	44644	4.2	9.6	33	88.4	27.9	31.3	9300	P46L46E4E2	Low Normal	Normocytic Normochromic	Erythroid Hyperplasia	11	9	24	36	4.6	2	2.6	5.2	3.2	2	98	95	84
50	45	M	44737	3.7	10.1	32	109	32.3	29.3	17000	P78L21E1	Low normal	macrocytosis target cells	Not done	4'0	5	16	22	5.8	3	2.8	1.6	1.2	0.4	38	27	73

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ABBREVIATIONS IN MASTER CHART

BT	-	Bleeding Time
CT	-	Clotting Time
PT	-	Prothrombin Time
APTT	-	Activated Partial thromoboplastin time
MCH	-	Mean Corpuscular Hemoglobin
MCHC	-	Mean Corpuscular Hemoglobin Concentration
MCV	-	Mean Corpuscular Volume
PCV	-	Packed cell volume
UGD	-	Upper Gastro duodenal Endoscopy
LFT	-	Liver function test
AST	-	Aspartate transaminase
ALT	-	Alanine transminase
SAP	-	Serum Alkaline Phosphatase
M	-	Male
F	-	Female
+	-	Present
-	-	Absent
T	-	Total
A	-	Albumin
G	-	Globulin
D	-	Direct
I	-	Indirect
Mod	-	Moderate